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NAVC CONFERENCE VETERINARY PROCEEDINGS

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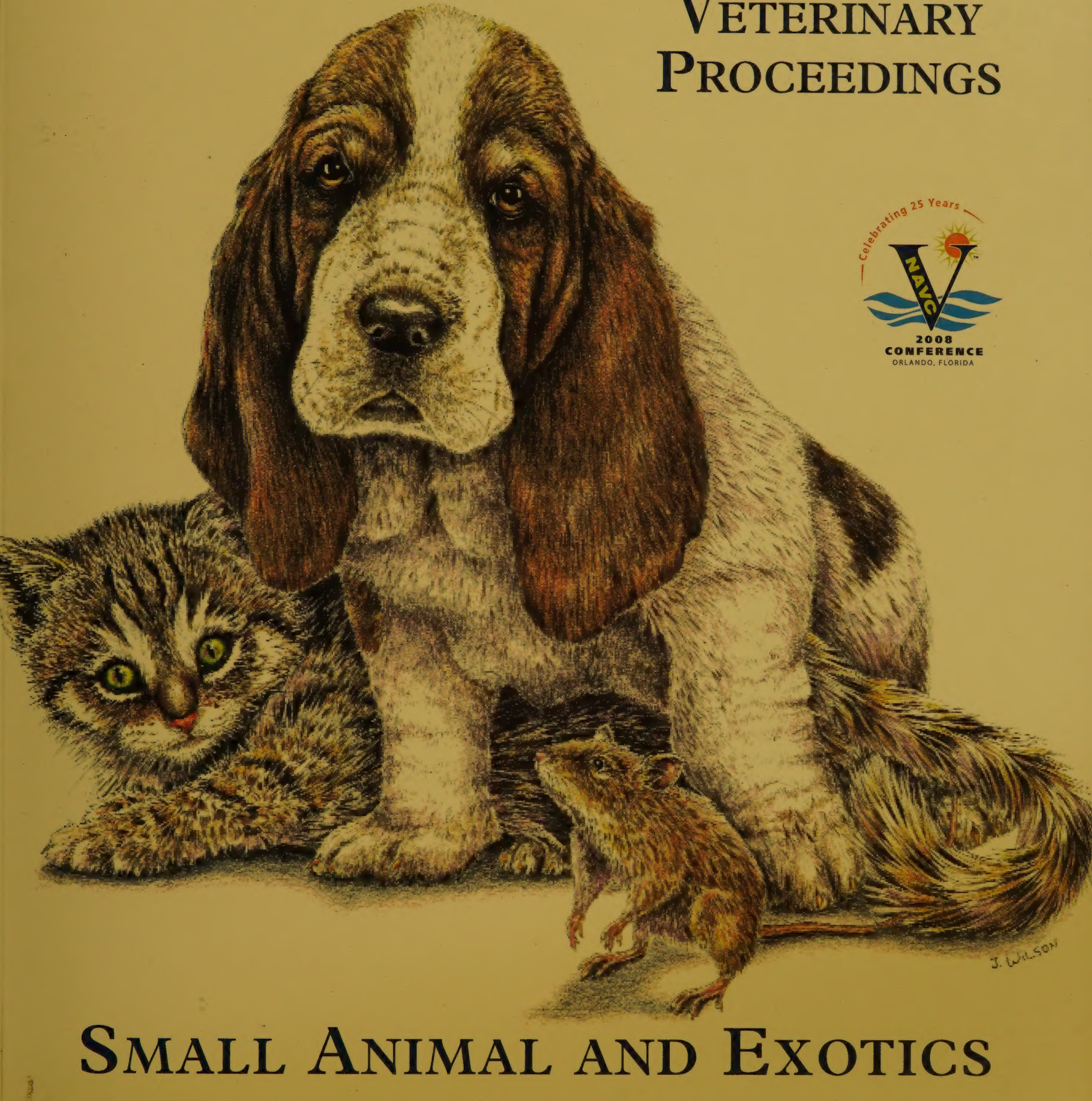

SMALL ANIMAL AND EXOTICS

ALTERNATIVE MEDICINE – OPHTHALMOLOGY

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BOOK 1

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While all contributors were invited to submit manuscripts for the general sessions, some chose not to do so. The NAVC regrets these omissions, but has done everything possible to ensure a comprehensive Proceedings for the NAVC Conference 2008.

"Special thanks for the assistance received from Robin Hipple, Medical Editor and Marcy Bryant, Layout."

About the Cover: **Jim Wilson's** fascination with animals has influenced many aspects of his life including his career choice. A professional wildlife artist for over thirty five years, Jim spends many hours seeking out and researching his subjects for his detailed pen and ink drawings. He relies on reference material gathered from field work, museums, zoos, veterinary hospitals and rehabilitation facilities. His camera is a constant companion, providing a permanent collection of reference photos. Jim's work has been featured in a variety of NAVC material since 1992.

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INTRODUCTION TO VETERINARY ACUPUNCTURE

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Veterinary acupuncture is believed to have been in use almost since the first records of acupuncture. The first written record of veterinary acupuncture is a treatise on the use of acupuncture on Indian elephants, estimated to have been written 3000 years ago. One of the oldest documents on Traditional Chinese Medicine (TCM) was published sometime between 400 and 200 BC, the *Huang Ti Nei Ching*, or *The Yellow Emperor's Classic of Internal Medicine*. It is considered the basis of TCM and describes the Oriental philosophy of anatomy, physiology, pathology, diagnosis, and treatment of maladies of that time. Included in TCM are acupuncture, moxibustion, Tui-Na (manipulative therapy or massage), Qi-Gung (breathing exercises), Shu-Shieh (nutrition and diet), and herbal medicine.[1]

Shun Yang (also called Pao Lo), 480 BC, was considered the first full-time practitioner of Chinese veterinary medicine on record. He is considered the father of the profession in China. Acupuncture was introduced in the West by a French Jesuit, P.P. Harvieu, who published the first European work on acupuncture in 1671. Acupuncture appears to have been introduced in the United States in the nineteenth century. In 1893, Sir William Osler mentioned acupuncture as a treatment for lumbago in the textbook *The Principles and Practice of Medicine.*

The International Veterinary Acupuncture Society (IVAS) was formed in 1974 to promote "excellence in the practice of veterinary acupuncture as an integral part of the total veterinary health delivery system." IVAS offers a certification exam and training courses throughout the world. Annual congresses are held where there is an international board of delegates that meets, as well as presentation of research papers and acupuncture techniques.

Veterinary acupuncture has become known as the use of needles in stimulating acupuncture points for the purpose of relieving pain or improving the function of various systems of an animal's body. In actuality, stimulation by needles is only one form of acupuncture; it also includes stimulating acupuncture points with finger pressure, heat, ultrasound, laser, aquapuncture, electroacupuncture, and implantation.

Histologically, acupuncture points are cutaneous areas supplied by relatively high concentrations of free nerve endings, nerve bundles and nerve plexi, mast cells, lymphatics, capillaries, and venules.[2] No unique structures are found at acupuncture points, but most are associated with neural structures: muscle motor points, foci of nerves overlapping in the sagittal plane, loci of nerve plexi or superficial cutaneous nerves. Approximately 70% of acupuncture points correspond to trigger points.[3] Acupuncture points can be objectively measured as areas of lower electrical resistance compared with the surrounding skin. Normal dry skin has a direct current (DC) resistance of 200,000 to 2,000,000 ohms, which decreases to approximately 50,000 ohms at acupuncture points.[4] Because of this electrical phenomenon, acupuncture point finders have been developed that measure resistance based on Ohm's law. Point finders are often used by students of acupuncture, until they have developed the feel for palpating acupuncture points.

Numerous studies have been done on acute pain in animals and humans. Acupuncture analgesia from needling true points is superior to sham points. Point specificity has not been well studied in the treatment of chronic pain, but in Pomeranz' study in patients with chronic pain, placebo effect was quite strong, working in 30% to 35% of patients, compared with 33% to 50% of those with sham needling and 55% to 80% with needling true points.

One of the theories that has been used to explain acupunctures effectiveness in analgesia is called the gate theory. It proposes that impulses in fast conducting, large diameter afferent nerve fibers conveying information about pressure, touch, and vibration to the dorsal horn, synapse on inhibitory interneurons that close the "gate" to the ascending pain transmission before the impulses arrive from the slowly conducting nociceptive fibers. This would prevent pain impulses from reaching the brain for perception. This theory does not address the continuation of analgesia beyond the cessation of stimulation. It is very likely that it works through an endogenous pain inhibitory system. This system involves descending impulses from the brainstem to the inhibitory complex in the dorsal horn, where it blocks pain impulses from being relayed to the brain. Endogenous substances such as enkephlins and seratonin are mediators in this system.

In order to do acupuncture, a practitioner must learn the anatomic location of acupuncture points and the physiologic consequence of stimulating each point, individually and in combination with other points. After making a diagnosis and determining that acupuncture is indicated, a practitioner must select the points to be used (prescription), establish the duration of the treatment session, and choose the type of stimulus.

In clinical practice, veterinary acupuncture is utilized for its diagnostic, therapeutic, and hypoalgesic properties. A thorough patient history is required for diagnosis according to Traditional Chinese Medicine (TCM), and is integrated into our Western thought and diagnosis. For example, an old pet may be presented that has difficulty getting up and it has been determined radiologically that the pet has extensive spondylosis in the lumbar spine and arthritis in both hips. In Western practice, this pet would probably be treated with non-steroidal anti-inflammatory drugs. As an important part of the history in developing a diagnosis for acupuncture treatment, it is also important to know other aspects of the problem, such as what is the energy level of the pet? Does the patient prefer to lie on the kitchen floor (cold surface) as opposed to the carpet? Does he prefer the warmth of the sun to the air conditioned room? How much water does he drink? Does he have a tendency to drink large quantities at a time? What is his appetite like? History of any past traumas or surgery? ...

Questions of this nature guide the practitioner in determining the energy of the pet, whether the condition involves heat or cold pain, and which treatment options might be useful. The health history can direct the practitioner to the constitution of the pet. Pain and arthritis are both considered to be due to the interruption of the flow of Qi through the affected area. Qi (pronounced "chi") is the name for the vital energy and nutrition that flows through our body. It is like a form of electricity that travels with the blood and through the tissues to keep the cells metabolizing at their optimum. If there was never an interruption in the flow, including the cellular level, there would never be buildup of osteophytes that cause arthritis. This is idealistic, for any type of trauma can cause an interruption of flow of Qi and cause pain. A bruise is a good example of the "stagnation of blood and Qi." Not only trauma can cause the decrease in the flow of Qi, emotional stress, deficiency of fluids, body confirmation, genetics, and deficiency of energy may also contribute to decreased flow. Acupuncture is a way to help direct the flow of Qi in the body. It cannot, however, significantly add energy that is not already within the body. It is an excellent way to tap into reserves within the body so that they can be utilized where needed. We derive energy through the food we eat, and the air that we breathe. The Chinese use herbal therapy and food therapy to aide in building energy as well as breathing exercises.

The acupuncture meridian system has been compared with an electrical system with dimmer switches along the way. Acupuncture points act as dimmer switches or relay switches that can regulate the flow of electricity or Qi. There are 12 main pairs of these complex pathways called meridians through which the Qi flows. Each of the 12 major meridians is associated with an internal organ and is like a power line running through the body. There are also two unpaired meridians that course the midline on the front of the body and the midline on the back of the body. For example, the Heart meridian starts in the area of the axilla and courses down the medial side of the arm and ends on the outside of the little finger by the fingernail. When someone is having a heart attack, sensation along this pathway is sometimes evident.

Applications in veterinary practice include:

- **Diagnostic tool**
- **Musculoskeletal system**
  - Intervertebral disk disease

  - Hip dysplasia – Basic point prescription:
    - GB29 - 1/3 the distance from the greater trochanter to the cranial dorsal iliac spine
    - GB 30 - Midway between the greater trochanter and the tuber ischii
    - BL 54 - Depression just dorsal to the greater trochanter
  - Promote bone healing
  - Muscular weakness
  - Arthritis
- **Neurological System**
  - Nerve trauma
  - Seizures
  - Wobblers
- **Miscellaneous**
  - Wound healing
  - Anestrus and other reproductive problems
  - Abdominal pain with enteritis
  - Inflammation
  - Decreased energy levels
  - Cancer patient support
  - In adjunct to current therapies in dealing with renal disease
  - Emergency Point: GV 26 - In the intersection of the "T" formed below the nose, in the filtrum

The most commonly used forms of acupuncture in animals are dry needling, aquapuncture, laser, acupressure, moxibustion, electroacupuncture, ultrasound, and implants.

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THE SMELLY, ITCHY DOG: A CASE REPORT

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A 6-year-old Scottish deerhound was presented for hair loss and itching, especially around the eyes and mouth, but also the ear pinnae. There was also hair loss on the backs of the hind legs. The owner had been giving prednisone 20 mg several times a week, but wanted to reduce the dosage because she had other deerhounds that had had problems on steroids.

On examination, there was hair loss on the face and back legs. The skin was mildly red and had an odor; the skin was thickened. The pulse was rapid and weaker than I would have expected for the breed. The tongue and gums were red, and the dog was panting. The face appeared to be more pruritic than the legs, but there was not much scratching in other areas. Appetite was good. The dog was fed a premium brand dry food and was on a fatty acid supplement.

SYMPTOMS:	**TCM**:
• Itching or pruritus	Wind
• Mildly red skin	Heat (deficiency or excess)
• Thickened skin	Damp or phlegm
• Odor	Heat or Damp Heat
• Rapid pulse	Heat
• Pulse not full	Deficiency (blood)
• Hair loss	Deficiency or phlegm
• Panting	Heat or nervousness

DIAGNOSIS

Deficiency heat with Wind and Damp

TREATMENT PRINCIPLE

- Eliminate Wind and Damp and Heat
- Nourish the Blood
- Move the Blood

TREATMENT FORMULAS

(Long Dan Xie Gan Tang)

Long Dan Xie Gan Tang, Jia Hua Ban Jie Du Tang - Itching

(9)	*10g RADIX GENTIANAE long dan cao	clear damp heat; itching
(12)	10g RADIX SCUTELLARIAE huang qin	drain and clear heat, toxic heat from skin
(12)	10g FRUCTUS GARDENIAE zhi zi	clear toxic heat and damp heat
(6)	10g CAULIS CLEMATIDIS oder AKEBIAE mu tong	drain damp heat and toxic heat
(15)	10g SEMEN PLANTAGINIS che qian zi	drain and clear damp heat
(12)	10g RHIZOMA ALISMATIS ze xie	drain damp and heat; nourish yin
(9)	RADIX BUPLEURI chai hu	disperse stagnation, ears
(15)	30g RADIX REHMANNIAE sheng di huang	tonify blood
(12)	RADIX ANGELICAE SINENSIS dang gui	treat blood def of skin
(6)	RADIX GLYCYRRHIZAE gan cao	clear heat from skin
	10g CORTEX MOUTAN RADICIS mu dan pi	soften blood stasis, replenish yin
	12g FOLIUM ISATIDIS da qing ye	drain damp
	12g PORIA COCOS fu ling	drain damp
	10g FLOS LONICERA jin yin hua	clear damp heat
	10g FRUCTUS FORSYTHIAE lian qiao	clear damp heat
	* 15g CORTEX DICTAMNI RADICIS bai xian pi	clear heat

After clearing the damp and heat from the skin, the inflammation had greatly decreased but the skin was dry and flakey. Hair regrowth was progressing. The formula was changed to one that addressed the deficiency of yin and blood, and the itching

(Huo Xue Qu Feng Tang)

Huo Xue Qu Feng Tang - Itching

(9g)	10g RADIX ANGELICAE SINENSIS) dang gui wei	replenish blood, disperse qi
(9g)	10g RADIX PAEONIAE RUBRAE chi shao	disperse blood stagnation, heat
(9g)	10g SEMEN PERSICAE tao ren	invigorate blood, soften mass
(9g)	10g FLOS CARTHAMI hong hua	remove heat, toxic heat; eyes
(9g)	* 10g HERBA SCHIZONEPETAE jing jie	remove blood deficiency wind; itch
(9g)	* 12g FRUCTUS TRIBULI bai ji li	remove blood deficiency wind; itch
(6g)	6g RADIX GLYCYRRHIZAE gan cao	clear heat from skin
	* 6g RADIX LIGUSTICI CHUANXIONG chuan xiong	remove wind from skin, disperses; itch
	* 6g PERIOSTRACUM CICADAE chan tui	remove toxic heat, wind heat, itch

Plus Envoy Herbs

6g RADIX ANGELICAE DAHURICAE bai zhi	nose, face; clear wind, damp, heat
4g CORTEX PHELLODENDRI huang bai	ears, face; clear damp, heat
6g FRUCTUS LIGUSTRI LUCIDI nu zhen zi	eyes; remove deficiency fire, nourish yin, hair loss

May Add Nourishing Herbs:

10g HERBA ECLIPTAE PROSTRATAE han lian cao	nourish blood, yin; deficiency hair loss
10g SEMEN SESAMI INDICI hei zhi ma	nourish blood; deficiency hair loss

Other popular formulas that are available are the Jing Tang Damp Heat Skin and Kan Herbs Veterinary Formula for Damp and Heat

The Jing Tang Damp Heat Skin:

SCUTELLARIA	huang qin	clear damp- heat; detoxify
PHELLODENDRON	huang bai	clear damp- heat; detoxify
SOPHORA	ku shen	clear damp- heat; detoxify; relieve itch
REHMANNIA	sheng di huang	cool blood and nourish yin
ISATIS	ban lang gen	clear heat, detoxify
PLANTAGO	che qian zi	clear damp- heat; benefit urination
TALC,	hua shi	clear damp- heat; benefit urination

Si Miao San

PHELLODENDRON	huang bai
ATRACTYLODES	cang zhu
ACHYRANTHES	huai niu xi
COICIS	yi yi ren

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VETERINARY APITHERAPY – OR THE THERAPY THAT STINGS

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Veterinary apitherapy is the medical use of honeybee products for the benefit of sick animals. It can include the use of honey, pollen, propolis, royal jelly, and bee venom, but most commonly refers to the use of bee venom, also called Veterinary Bee Venom Therapy (VBVT), which is the application or injection of the honeybee (*Apis mellifica*) venom. In this article, we mean Veterinary Apitherapy in its narrow meaning, that is to say, Veterinary Bee Venom Therapy (VBVT).

Ancient writers such as Aristophanes (450–388 BC), Hippocrates (460–377 BC), Galan (131–201 AD), and Charlemagne (742–814 AD) wrote about the medical use of honeybee stings. The Koran refers to bee venom as "liquor wherein is a medicine for men and animals." In 1835 the Reverend Brauns of Germany begun using diluted bee venom in different domestic animals, and later on in 1853, Dr. Constantine Hering introduced the homeopathic use of BVT in the US. About 100 years ago, the physician Dr. Terc of Austria advocated the deliberate use of bee stings for rheumatism. In 1935, Dr. Beck from US introduced apitherapy as we know it today for multiple medical uses.

Bees produce approximately 0.1 mg dried venom per venom sac. It can be introduce intradermally by live bees, or by injection of an extract.

In every 0.1 mg of bee venom there are about 40 different components that are water-soluble. The main anti-inflammatory pharmacologic components are peptides: melittin, apamin, peptide 401, adolapin, and protease inhibitors. Melittin stimulates the hypophyseal-adrenal system and produces cortisone. It is 100 times more potent than hydrocortisone. Melittin also stabilizes the lysosome cell membrane to protect against inflammation. Apamin works like melittin to produce cortisone, and inhibits the complement system, C3, which is involved in inflammation, as well as enhancing nerve transmission. Peptide 401, or MDC peptide, blocks the arachidonic acid and inhibits prostaglandin synthesis. Adolapin inhibits the microsomal cyclo-oxygenase. It is 70 times stronger than indomethacin in animal models, and has analgesic as well as anti-inflammatory properties. It also inhibits platelet lipoxygenase, which involves hydroperoxy-eicotetranonic acid (HPETE), and leukotriene, as well as inhibiting thromboxane (TXA2) and prostacycline (PGI2), which are activated during inflammation. Protease inhibitors inhibit carrageenin, prostaglandin E1, bradykinin, and histamine-induced inflammations; they also inhibit chymotrypsin and leucine-aminopeptidase. Other substances such as Compound X, hyaluronidase, phosphlipase A2, histamine, and mast cell degranulating protein (MSDP), are involving in the inflammatory response of the venom, with the softening of the tissue, and the fascilitation of the flow of the other substances. Finally, there are measurable amounts of neurotransmitters as dopamine, serotonin and norepinephrine. Many reports claim that bee venom has strong antibacterial and antifungal effects.

The clinical uses of apitherapy are numerous: alleviation of many acute or chronic ailments as inflammation and/or degeneration of connective tissue (eg, tendonitis, bursitis, different types of arthritis), osteoarthritis as in canine hip dysplasia, neurologic wasting diseases affecting the limbs (as degenerative myelopathy), neurologic diseases such as peripheral neuritis or radiculitis, chronic pain conditions, autoimmune diseases (eg, lupus), and dermatologic conditions (eg, atopic dermatitis, warts) and scar tissue therapy. Hypogalactica postpartum syndrome in sows is also responsive to VBVT, which is done using bee-acupuncture technique.

Bee venom softens scar tissue and causes scars to fade. Internal scar tissue, such as adhesions resulting from surgery, may also respond to treatment with bee venom.

According to Traditional Chinese Veterinary Medicine (TCVM), we use VBVT for Wei Syndrome (or Wei Bi). Wei syndrome is characterized by weakness of the limbs, which leads to atrophy, flaccid muscles and tendons, and eventual paralysis. This condition generally progresses without pain. We apply VBVT to local and adjacent points, distal and proximal points on the same meridian, and empirical points. The use of VBVT is contraindicated in any pregnant animal, in the presence of any cancerous tumor within 10 cm of the treated site, in patients with any known and demonstrated allergies to honey bee venom, proximity within 10 cm to surgical implant, or in animals on pharmaceuticals that suppress the immune system. It seems that VBVT has reduced benefit in animals with diabetes mellitus.

Side effects of bee venom are generally limited, since the inflammation, swelling, itching etc. are desired effects and usually disappear without further intervention in anywhere from a few to 72 hours. However, the risk of anaphylactic allergic reaction to bee venom is real, and it always wise to have a bee venom sting allergy kit on hand. Fortunately, most "bee" sting allergic reactions are actually to yellow jackets or wasps. Honeybee venom does not necessarily cross-react, and it seems as only 5% of all adverse reactions to insect stinging are related to honeybee stings. Keep in mind that many animals that have had severe local reactions to bee stings, which we consider a positive effect, are incorrectly considered to have allergy to bees.

In the first visit, after evaluating whether VBVT should be applied to the treated animal, as well as contra-indications mentioned before, obtain a written, witnessed informed consent, have with you a preloaded syringe of epinephrine (Bee Sting Kit, Epipen >30 kg animal body weight, Epipen jun <30 kg) and a clinic emergency set-up, press an ice cube against the target site firmly to animal tolerance for 15 to 45 seconds, and apply VBVT to only one site.

The animal must be observed for 10 to 20 minutes. Animal to be excluded from VBVT are those that have systemic reactions such as generalized itching, rashes, short of breath, fever and possible anaphylactic response, or the local reactions are more than erythema greater than 2 cm in diameter and/or wheal greater than 1 cm in diameter. If only local reactions are seen for 20 minutes, the animal's owner is asked to come back for the next therapy session in 72 hours. In a very agitated animal we might consider to put the animal in advance on a light sedative before the application of the sting. Explain to the owner the need in certain cases to use an ice cube locally to calm the animal.

The routine protocol for using VBVT in animals is done by pressing an ice cube firmly against the target site to animal tolerance for 15 to 45 seconds, or infiltrating the area with local anesthetic such as lidocaine 2% without epinephrine to begin with.

Second, extract the bee with long pair of tweezers. Place the posterior aspect of the bee on the desired spot and administer the sting. The bee would then be discarded. Another approach is to eviscerate the bee by pulling the stinger and its attached venom sac from the live bee. The other method is injecting bee venom from a sterile vial (see below).

The number, site, and frequency of stings depend on the treated animal and the clinical problem. A simple tendonitis might just take a few stings, perhaps 2 to 3 at a session for 2 to 5 sessions. A more chronic problem like chronic arthritis can take 2 times per week, several stings at a time, for 1 to 2 months.

Since the immediate effect of bee venom does not last longer than 2 to 3 days, the animal is requested to return after 3 days for further evaluation and therapy.

Never sting on an unresolved previous site. Use a different spot, or wait till the sting has resolved (1 to 3 days). Do not add more than three new sites per visit.

For the injectable bee venom technique, there are sterilized vials on the market. The bee venom can be injected intradermally into the selected points using a 30-gauge needle.

The injectable bee venom dried extract ("Apitox/Apitoxin") containing 1 mg dried venom is diluted in 1 mL 0.9% saline, to give 0.1 mg/0.1 mL = 1 bee sting, or it can be diluted with lidocaine 2% without epinephrine. For every site, we can inject 0.1 mL.

Since we might need to inject many points in one session, it might be a good idea to dilute the 1 mL mother solution into 9 mL saline, and inject into each point 0.2 mL = 0.02 mg of dry bee venom toxin (with lidocaine). Many times we inject the remedy deep into the tissues. For example, for a prolapsed disk we might go 1 cm or more deep into the tissues.

The advantages of the injectable technique include the fact that it is a quantitative procedure, the hypersensitivity issue can be avoided by dilution, and it is a human procedure (as far as collecting venom from bees), available any time and location. A disadvantage is that some of the potency might be lost (the extraction of the bee venom and subsequent desiccation results in a loss of all aromatic substances and about 25% of the greasy acids, and hence a decrease in its medical qualities).

It is important to note that some clinicians dilute the venom homeopathically 3x to 5x, and inject it in the usual way, or into acupuncture points, thus reducing the cost, as well as chances of adverse reactions. In chronic therapy (months), the animal might enter "a reactive phase." The animal's reaction to the venom will be intense. That is a good healing sign, but we might need to add local infiltration of lidocaine to alleviate the animal's discomfort. This phase is very critical time in the entire therapeutic process. At some point things will calm down, and then the therapy can be stopped.

NEUROPATHY TREATED BY BEE VENOM THERAPY

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A 6-year-old spayed female Golden Retriever was presented to our clinic with acute unilateral left side facial paralysis. The following clinical signs were noted: paralysis of left eyelid; with saliva and food fallen from the same side; nasal philtrum deviated to the normal (right) side; widening of the palpebral fissure with failure to close upon excitation; asymmetry of facial expression, and no signs of involvement of other cranial nerves or other nerve system signs. Otitis media was not observed.

A tentative diagnosis of idiopathic facial paralysis was given, with the probable site of the lesion at the facial nucleus (rostral medulla oblongata of the brain stem) or proximal portion of the facial nerve.

Therapy consisted of application of artificial tears a few times a day to the affected eye and injection of bee venom into acupuncture points.

Twenty micrograms of bee venom with 0.2% lidocaine without epinephrine were injected twice a week for 2 weeks for each of the acupuncture points on the affected side. Two weeks later the dog's facial nerve began to return to normal activity, and dog appreared normal 4 weeks after the start of therapy. Acupuncture points were: ST 02, ST 04, ST 06, SI 18, TH 17, GB 20.

FELINE THROMBOEMBOLISM (SADDLE THROMBUS) TREATED BY MEDICAL LEECHES

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A 2-year-old short-haired domestic spayed female cat was presented to our clinic with acute hind limb paralysis with pain in these extremities, lack of a palpable femoral pulse in both legs, cold and blue distal limbs, and lack of bleeding from cut nail beds.

The owner refused to authorize us to perform ancillary tests and asked for a simple and inexpensive therapy. Two medical leeches (*Hirudo medicinalis*) were applied to the each side of the inner side of the thigh close to the abdomen.

Leeches were removed 20 minutes after application. Twenty-four hours later the cat regained almost complete normal walking abilities, was free of pain, and had normal femoral pulses.

This cat was seen and treated in December 2005. The cat has been seen in our clinic a few more times since then and has a normal life. We have had a few similar cases in the past 2 years and all of them responded well to therapy with medical leeches.

EVIDENCE-BASED ACUPUNCTURE

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During the last few years (1999–2007) we have treated four different cases of canine intracranial blindness (also known as cortical blindness) due to head trauma in hit-by-car situations in our clinic. We used identical protocols for all four cases, and achieved a complete return of vision abilities in a short period of time (within 24 hours). A similar clinical case (a fifth case) was treated at the same period of time in a US-based veterinary clinic with the same protocol given by us and with same clinical result.

The basic protocol that was done:

1. Treat the dog for all other conditions involved in the trauma
2. Diagnosis of intracranial blindness by a certified veterinary ophthalmologist
3. Treat the blindness by routine advised pharmacological methods (steroids, etc.) for 10 days
4. If the dog can not see during and after 10 days, consider performing electro-acupuncture protocol
5. The acupuncture points are ST-01 in a calm dog, but in a more active dog consider ST-02; the second acupuncture point is SI-18. Thus, we are going to use either ST-01 or ST-02 and the second acupuncture point will be SI-18.

ST-01: Cheng Qi, Receiving Tears

- **Location**: In the center of the ventral border of the orbit, between the globe of the eye and the orbital rim (zygomatic arch)
- **Location method**: There is a small notch in the orbital rim. Also, directly below the center of the pupil between the eyeball and infraorbital ridge
- **Characteristics**: Local point that expels exterior and interior Wind from the eye
- **Indications**: Conjunctivitis, atrophy of the optic nerve, retinitis, cataract, any other eye disorder including intracranial blindness, stroke
- **Method of insertion**: Press the eyeball dorsally, and insert the long needle gently to the depth of 0.5–2 cm. along the border of the orbit. This acupoint should be done only by an experienced acupuncturist due to the danger of puncturing the eye!
- **Need a good restraint of the dog.** *For head Blood Stasis therapy might go deep up to 5 cm until you hit the palatine bone.*

ST-02: Si Bai, Four White

- **Location**: Directly below ST-01.
- **Location Method**: Directly below the pupil, ventral to the orbital ridge of the zygomatic bone
- **Characteristics**: Expels exterior and interior Wind from the eye. Relaxes tendons and muscles, smoothes Qi & Blood circulation
- **Indications**: Facial paralysis, conjunctivitis, mandibular myositis, maxillary teeth problems, gingivitis, intracranial blindness, stroke
- **Method of insertion**: Perpendicular insertion 0.5–2 cm, or up to 1 cm if with angular insertion. *For head Blood Stasis therapy might go deep up to 5 cm until you hit the palatine bone*

SI-18: Quanliao, Zygoma Crevice

- **Location**: Directly below the outer eye canthus and below the lower border of zygomatic arch
- **Characteristics:** Expels exterior & interior Wind from the face and eye
- **Indications:** Facial paralysis, trigeminal neuralgia, conjunctivitis, mandibular myositis, maxillary teeth problems, gingivitis, intracranial blindness, stroke
- **Method of insertion:** Perpendicular insertion 0.2-0.5 cm, or up to 1 cm if with angular insertion. *For head Blood Stasis therapy might go deep up to 5 cm till you hit the*

Insert the needles bilaterally, begin with 1 Hz, elevate gradually up to 10 Hz, A/C mode, 5–10 Volts, 6 mA, intermittent mode for 20 minutes.

Evaluation of a successful insertion of the needles is done by evaluation of increased production of eye tears and nasal drops appearance—this can be seen after 10 minutes of stimulation and at levels above 5 Hz. If no drops are seen, change the location of needles. Total time of stimulation is 20 minutes. Re-evaluate the vision ......abilities during the next 48 hours.

If no improvement is seen during this period of time, re-treat the animal. Also, one can stimulate for 20 minutes, stop for 20 minutes, and re-stimulate. This procedure can be re-done a few times in the time period of the mentioned above (48 hours).

So far, we have not found non-responders, but they are expected and will be documented.

Subsequently, an Israeli biomedical company ("Brainsgate") heard about my work and asked me to join the company medical advisor team. Suddenly I had on my team some of the best human medicine Israeli neurologists, neurosurgeons, and neurophysiologists, and I had now hoped to be able to find the anatomic as well as the physiological mechanism behind my work.

The anatomic distribution and functional role of my acupuncture stimulation is well known for the last 80 years in the scientific and medical communities. More and more data is collected every year for the last two decades using up-to-date medical tools (CT, MRI, angiograms, modern histologic techniques, etc).

As I was inserting the needles to these specific locations I stimulate the sphenopalatine ganglion (SPG), also known in dogs as pterygopalatine ganglion. This ganglion is part of the parasympathetic system.

The preganglionic parasympathetic fibers originate in the superior salivatory nucleus and travel first with the facial nerve, and then alone, as the greater superficial petrosal nerve and then the nerve of the pterygopalatine canal or vidian nerve. The latter reaches the SPG, residing in the SPG fossa, where the fibers synapse, or if you wish, in dogs, the pterygopalatine ganglion in the pterygopalatine fossa. The preganglionic neurotransmitter of these fibers is acetylcholine, which acts on nicotinic postganglionic cholinergic receptors. The postganglionic fibers reach the cerbral vasculature, in addition to the lacrimal gland, forehead skin, eye mucosa and nasal mucosa (what explains why upon SPG stimulation we see eye drops and nasal drops). Fibers from each SPG ganglion innervate the ipsilateral hemisphere, and that is why a bilateral stimulation is needed. The stimulation is leading to vasodilatation of the ipsilateral cerebral arteries and augments cerebral perfusion even if initiated within the first 21 days following brain ischemic cases. The increased blood flow to the brain is expected to increase collateral blood flow, bypassing the blocked section of the cerebral artery and bringing oxygen to damaged areas of the brain. The neurotransmitters released by the postganglionic fibers include nitric oxide (NO), vasoactive intestinal polypeptide (VIP), and acetylcholine as well as others.

The role of nitric oxide is not only to reduce the infarct size after local ischemia, but also to promote neurogenesis in the adult brain and promote rehabilitation.

An additional finding is that upon stimulation of the SPG we temporarily increase the permeability of the blood–brain barrier.

Another point that should be mentioned is that there are many intraocular projections/branches from SPG, and it means that even improper location/insertion of the needles might have achieved a clinical result.

CONCLUSION

in the last 80 years, a great deal of scientific and medical work has been done regarding the anatomy and physiology of our specific protocol. According to Thomas Kuhn in his book, *The Structure of Scientific Revolution,* one can see that most of CAVM has different paradigms from the modern western medicine. It is important to understand the nature of paradigms, including the appropriateness of assessing one by the other.

No paradigm is a complete one, being unable to answer all the questions that can be asked of it. Paradigm is not associated with truth; it involves methodologic approach towards problems. Different paradigms have different frames of references, and one paradigm cannot be translated into another. For example, Newton's Laws are not simply a special case of Einstein's theories of relativity, or can we translate the Chinese term "Qi" into "Energy" of the western world? Qi (like Yin & Yang) is a fundamental and complex concept which cannot be understood without taking into account the totality of the theoretical foundation and practice of Chinese medicine in addition to the Chinese worldview. Meridians are referred in western terms as two-dimensional passageways, but in TCM they are looked as three-dimensional passageways through which Qi and Blood flow at different levels of the body. Is it inappropriate to refer to the channels by using two-dimensional terms? There are many other fundamental examples.

Because of the incommensurability of paradigms, any CAVM practiced its original way cannot be the same as its biomedical version – they must stay two separate ways. If the biomedical paradigm is adopted, it will have its characteristics—materialistic, mechanistic, reductionist, linear-causal, and deterministic, and in short, "Yin and Yang do not exist" will be unavoidable.

Also, the questions and answers are different in the different paradigms. A CAVM clinician will recognizes conditions that are hard to diagnose in biomedical terms, and if the paradigm will be changed, this ability will be lost forever. We should insist that our own paradigm be given full recognition and acceptance.

A NOVEL APPROACH TO VETERINARY DERMATOLOGY

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Chinese physicians working from the beginning of the Ming dynasty (1368–1644 C.E.) through the Qing dynasty (1644–1911 C.E.) developed what became known as the pattern of four levels (*wei-qi-ying-xue bian-zheng*). Taking from the *Nei Jing* they described four sequential physiological entities/scenes; each one of them represents a different distinct depth of body's pathology.

The first level, called the **pattern of Wei Qi** (wei-fen-zheng), occurs at the first depth of the body, from the level above the skin (fur coat, flora on the skin, sweat, sebum, IgA from the animal's saliva, etc.) and extends inward through the stratum corneum, stratum granulosum, and to the upper part of the stratum spinosum of the epidermis.

The second level, called the **pattern of Qi** (qi-fen-zheng), occurs at the second depth of the body, from the lower part of the stratum spinosum to the basal layer (stratum basale) of the epidermis, referred to collectively as the stratum germinativum or Malpighian layer.

The third level, called the **pattern of Ying** (ying-fen-zheng), occurs at the outer two thirds of the dermis. The word ying describes the Nutritive aspect of Qi that is associated with Blood and mainly with extra-cellular fluid.

The fourth level, called the **pattern of Xue** (Blood) (xue-fen-zheng), is the final and deepest of the four levels. It is the lower part of the dermis, in the lower blood plexuses and in the hypodermis.

According to this specific concept, one should look on animal's skin and asks: "At what level the lesion can be found?"

Acute moist dermatitis due to flea bites ("hot spot") might be in the Wei Qi level. When one is presented with chronic ulcerative dermatitis due to an immunological condition such as discoid lupus erythematousus, one can see that the lesion is deep into the Xue level. In cases of lichenification and hyperpigmentation, the lesion might be in the Ying level.

The answer can be found by simple observation without any specific advanced tools, or one can use histological preparations or other advanced methods to assist in making the determination of the lesion's location.

By making the determination of the lesion location we are making our diagnostic process easier. It will also allow us to set up our therapeutic goals; for example, for lichenification and hyperpigmentation due to a lesion at the Ying level one should nourish the Yin, etc.

We will also be able to give a prognosis and realistic timetable for healing: the healing time for a Wei Qi level problem will be a few days and prognosis is excellent. If the lesion is deeper, the healing time will be longer—from weeks to months—and the prognosis for complete cure also worsens when the process is deeper.

One will also have better understanding of the pathology and pathogenesis of the pattern.

As part of this new approach we are going to look for other acupuncture points compared to what we used in the past (for example, Blood-related points for Xue level issues, as BL 17, LU 9, etc.) and new herbal formulas (for example,. for Ying & Xue levels issues, formulas for clearing Heat from Ying level, invigorating Blood, etc.).

One can adopt the four levels concept regarding dermatological conditions and work up clinical cases successfully. We can expand our abilities by adding the six stages concept to the working-up scheme of skin conditions.

Zhang Zhong-jing, one of the greatest physicians in Chinese history, developed in his classic book *Shang-han Lun* ("Discussion of Cold-induced Disorders", written around 220 C.E.) the idea of six stages pattern (*liu-jing bian-zheng*). The ideological background is taken from the *Nei Jing* that describes six disease stages. The six stages presented in his book comprise a series of patterns that map out the course of diseases.

Dr. Zhang suggests that diseases begin with the first stage and proceed in sequence to the sixth stage; however, a disease can go straight to any stage, skip stages, or even move in a reverse way.

The first stage is called ***Tai Yang*** (Small Intestine and Bladder stage). Second, the disease might enter either ***Yang Ming*** (Large Intestine and Stomach) or the ***Shao Yang*** (Triple Heater and Gall Bladder) stage.

Yang Ming will mark the internal development of the disease.

Shao Yang is known as a half-Exterior/half-Interior pattern, and should be therefore before *Yang Ming*; however, based on the original *Nei Jing* concept it appears after *Yang Ming*.

These first three stages, ***Tai Yang, Yang Ming,*** and ***Shao Yang***, are patterns of Excess. The next three stages are patterns of Deficiency and Interiority.

The fourth stage is ***Tai Yin*** (Lung and Spleen), the fifth stage is ***Shao Yin*** (Heart and Kidney), and the sixth stage is ***Jue Yin*** (Liver and Pericardium).

It is common in dermatology to place the four levels and six stages one beside the other, which helps us to expand our diagnostic and therapeutic abilities (Table 1). This step directs the clinician not only to a better understanding of the process involved, but allows for a better selection of goals, acupuncture points, and herbal remedies.

To improve our abilities in the application of traditional Chinese veterinary medicine (TCVM) herbal remedies to animals I would like to introduce another concept, the third and last one in this article—transdermal herbal gel or foam. My suggestion to all of you – by putting your Chinese herbal remedies in transdermal gel or foam you are going to dramatically increase your clinical success rate.

Table 1. Pattern of the Four Levels and the Six Stages of Disease

Four Levels	Six Stages
Wei Qi Level	Tai Yang (SI+BL); Yang Ming (LI+ST)
Qi Level	Shao Yang (TH+GB); Tai Yin (LU+SP)
Ying Level	Tai Yin (LU+SP)
Xue Level	Shao Yin (HT+KID); Jue Yin (LIV+PC)

Advantages of using transdermal gels or foam include:

- No need to give pills, capsules, or tinctures, thus avoiding fights with the treated animal, or causing mental or physical trauma to the treated animal or the owner
- Good cosmetic qualities, as there is no visibility, no smell, and no residues on the skin, avoiding sticky or greasy feeling, and avoiding rubbing on carpets, furniture, clothes, etc.
- Potential for in-clinic manufacturing
- Ability to apply remedy to large surface area
- No lag time
- Cost effective
- Less irritation associated with occlusion or reaction to adhesives
- Absorption is done within less than one minute – so no need for neck collars or other protective measures to prevent the animal from licking or rubbing the remedy
- Excellent skin tolerability and nontoxic
- Uniform absorption
- The remedy forms a reservoir in the epidermis and enables once-a-day application
- The high water content provides good moisturizing properties

Disadvantages of using transdermal gels or foam include:

- Not appropriate if remedy needs activation in the gut
- Owner needs to put gloves on to apply or have a topical syringe

Note: Gels should be protected from sunlight and heat, and kept out of reach of children and animals.

HEMOACUPUNCTURE, OR THE THERAPY THAT STICKS

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In the last few years there has been a tendency in many parts of the international veterinary acupuncture community to work up a therapeutic plan using a Deficiency pattern. Many are citing from the *Nei Jing*: "The normal doctor treats thousands of symptoms (by using local and symptomatic treatment), the good doctor treats the underlying Excess, but the superior doctor treats the underlying Deficiency." But when one is dealing with Blood Stasis/Stagnation one should keep in mind also other cites from the same book:

- "If there is a stagnation it should be resolved by bloodletting before acupuncture and/or moxibustion."
- "If stagnant blood is not moved, new blood can not engendered."
- "Disease will not develop into a critical condition if the Blood keeps flowing."

WHAT ARE THE TCVM THEORIES AND MECHANISMS BEHIND THE NECESSITIES AND THE EFFECTS OF BLOODLETTING?

Direct Effects:

- Frees the flow of Qi
- Resolves Blood Stasis
- Clears Vacuity and Replete Heat
- Clears Blood-Heat
- Releases toxicity

Indirect Effects:

- Supplements Qi
- Nourishes and regenerate Blood
- Extinguishes Wind
- Calms the Shen
- Promotes sleep

History and Clinical Signs of Blood Stasis:

- History of external injury
- History of reproductive problems
- History of psycho-emotional disorder
- Enduring disease
- Variable energy level, tiredness better w/activity or movement, depression, moodiness, sighingLocalized sharp and constant stabbing painPain worse at night
- Pain's arc
- Itching with discolored skin patches, lesions might be chronic and raised, also ulcerated, coat is withered and yellowish, nails withered and/or falling off, peeling of abdominal skinHard, well-defined, immobile or fixed, possibly tender or painful lumps or masses, including organ enlargement, lumps/masses that may bleedLegs tremors, up to numbness or hemiplegia
- Purplish/blue lips
- Bloody stool/urine with bleeding of dark purple/brown/black clotted blood
- Pulse – choppy, regularly interrupted, deep or fine
- Tongue – purple spots/patches on tongue up to dark, brownish or engorged red tongue
- Purple blood vessels in the eye's sclera, bluish eyelids

Contraindications for Bloodletting Therapy:

- Coagulopathy or animal on anticoagulant therapy
- Anemia and/or low blood pressure
- Last stages of malignant tumor
- Pregnant animal
- Bleeding in estrus time

What Points Do We Bleed?

- Local & painful points
- Distal & proximal points of the affected meridian
- Jing Well/Ting points for specific problems according to the affected zang fu organ/meridian
- Treat LIVER points (LIV-02/03/14), BL-18, GB-34 to move Qi & Blood
- Treat HEART points to benefit Heart function of controlling Blood
- Empirical points as BL-17
- Around the ears pts (for head issues)
- GV-14 for pink eye, conjunctivitis, retinal atrophy
- GB-21, TH-15 for stiff neck/shoulders
- LI-15, TH-14 head-skin disorders
- Between shoulder blades for chronic gastritis & respiratory issues as asthma & bronchitis
- Uro-genital issues or mastitis – inguinal area

WHAT ARE THE TOOLS TO BE USED?

Medical Leeches *(Hirudo medicinalis)*

Why? Medical leeches are the best equipped creature on our globe to locate a point in Excess, especially a point with Blood Stasis/Stagnation, and that due to the fact that all their existence is about locating this point in Excess.

Additional benefits will be that we can work our way back in the Ko cycle, and use the leeches as a diagnostic tool for finding the Zang-Fu organ or meridian in Deficiency, and treat these points later. Also, due to the bacteriostatic and anesthetic abilities of the medical leeches, we can apply them to an acupuncture point or a tissue to be treated that is infectious and heavily contaminated area, and also a very painful area.

The use of medical leeches (Veterinary hirudotherapy, or VHT) is one of the oldest recorded veterinary medical treatments. The routine practice led patients to refer to their physicians as "leeches" (see current or old editions of Oxford Dictionary).

In the 20th century there was a marked decline in the use of medical leeches. Toward the end of the 20th century and at the beginning of the 21st century, there has been a medical shift to the re-use of medical leeches, and on June 28, 2004, the FDA cleared medicinal leeches for marketing as a medical tool. In November 2004, the journal *Nature* reported that 80% of Britain's 62 plastic-surgery units had used leeches postoperatively in the past 5 years. Leeches (*Hirudinea*) are slippery hermaphrodite bloodsucking worms with segmented bodies. They belong to the same large classification of worms as earthworms and certain oceanic worms (Annelids). Leeches can be found in freshwater lakes, ponds, or rivers with body size from 0.2 inch (5 mm) to nearly 18 inches (45 cm). Leeches consume the blood of a wide variety of animal hosts, ranging from fish to humans. There are over 650 known species of leeches, but the leech most commonly used is the European Medical Leech (*Hirudo medicinalis*). The leech has two characteristic suckers at both ends that attach jointly to the tissue while feeding. The mouth has three sharp jaws that leave a Y-shaped bite with some 100 tiny teeth on each jaw. A leech is an efficient bloodsucker. When attached, it can suck 5 mL of blood, an amount that is six to ten times its body weight, usually within 10 to 30 minutes. After its blood meal the leech falls from the tissue.

As the worm bites, it injects a complex cocktail of proteins into the host through its saliva, which are responsible for the therapeutic effects as well. The saliva contains Hirudin, a potent anticoagulant that consists of 65 amino acids. Hirudin inhibits the conversion of fibrinogen to fibrin by inhibiting thrombin & preventing blood from clotting. Hirudin also inhibits platelets aggregation. Hirudin works in conjunction with a vasodilator, one that increases the diameter of blood vessels by relaxing the smooth muscle of the blood vessels, to widen the diameter of the vessel and increase the flow of blood and by that promotes blood flow. The leech's vasodilator is a histamine-like substance. The effectiveness of this therapy is not simply due to enhanced blood flow, but because bleeding from a bite may continue as long as 10 hours, relieving tissue congestion mainly due to venous insufficiency, in areas where arterial flow is maintained but venous return is severely compromised, until collateral circulation reestablishes sufficient venous return in 4 to 5 days.

The frequency of the therapeutic sessions can vary from once for a sole day up to a few consecutive days to once every couple of weeks. Destabilase and hyaluronidase help breaking apart any fibrin fibers and local connective tissue and by that facilitate continual blood oozing from the leech's wound. Leech saliva contains a local morphine-like analgesic substance, allowing a painless attachment and feeding. An animal bitten by a leech may not even be aware of it until afterwards. Leech's saliva contains natural bacteriostatic component, as well as some regenerating and immunomodulatory substances. The saliva contains at least one anti-inflammatory molecule called leech-derived tryptase inhibitor.

What are the classical/western uses of medicinal leeches? Medicinal leeches applied to congested or inflamed parts of the animal body for over 3,500 years. They were used for engorged blood vessels as in acute equine laminitis, canine aural hematoma, swollen testicles, laryngitis, canine prolapsed rectum or bovine prolapsed uterus and inflamed vulva. Today, leeches are used also in reconstructive surgery on swollen faces, limbs, and digits following successful arterial re-vascularization but limited venous repair. Leeches are also used in the treatment of such disorders as inflammation and peripheral venous and arterial diseases as in cat's saddle thrombus. Leeches are also used to treat inflammatory and traumatic processes such as keratitis, chorioretinitis, periorbital hematoma, subretinal hemorrhage, glaucoma and cataract.

Leeches are being used to treat inflammatory diseases of the ear, nose and throat such as acute and chronic otitis, sinusitis, aural hematoma, and laryngitis, and to treat clinical forms of dermatitis and dermatosis (eg, eczema, paronychia, acral lick dermatitis). Leeches can be used to treat acute and chronic inflammatory immune-associated oral mucosa and peridontium lesions as in FIV-positive cats with severe stomatitis and gingivitis, diseases of the salivary glands as sialadenitis and sialoadenosis. Furthermore, leeches are used to treat inflammatory conditions of the urogenital tract as endometritis, dysfunction and injuries of the genital organs in postoperative rehabilitation.

Leeches are used to rehabilitate animals with postpartum pyo-septic complications. Hirudotherapy was also found to be effective in healing intractable and non-granulating wound or ulcers, especially in elderly and immunocompromised animals.

Leeching has been used as well for treating cats with polycythemia vera, or to reduce scrotal edema post-castration procedure in adult dogs. Recent studies suggest that leeches can lessen the pain of osteoarthritis and restore lost mobility as in canine hip dysplasia cases or knee osteoarthritis. Keep in mind that osteoarthritis is more than a disease of joint's wear and tear, it is also a vascular disorder. Small clots can occur in the blood vessels supplying bone and joint, and starve the tissue for oxygen. Chemicals that thin the blood and break clots apart could ease animal's misery as well as assisting in regeneration.

Once leech therapy is chosen, the clinician contacts one of many companies now spread all over the country to place an order for *Hirudo medicinalis*.

The leeches will come a container with non-chlorinated water. Some companies will add some salts or gels for better housing of the leeches. To store leeches in the clinic, use non-chlorinated water. No more than 50 leeches should be placed in a 2-gallon container. A tight-fitting lid is a necessity when housing the leeches to avoid escape. Lid perforations for air venting are advised. Leeches should be kept cool, not above 68°F (20°C), and avoid direct sunlight. Leeches can be kept for up to 3 months in un-fed condition. Change of suitable water is needed once a week.

Before applying the leeches, the area to be treated should be cleansed with clean non-chlorinated water. Remove any traces of povidone-iodine (Betadine) or any other skin preps. These traces may discourage the leech from attaching. Leeches should be applied in adequate numbers to the general area of maximal congestion or other treated area/tissue. One or two leeches may be sufficient to treat an area of 5 square cm. Move the container of leeches close to the patient. Wearing non-sterile gloves, take a long pair of non-toothed forceps in one hand and carefully lift the lid of the container. Be prepared to see some leeches clinging to the sides and even the lid of the container. Try to quickly but gently grasp a leech and remove it from the container. Leeches are very elastic and slippery and this combination makes them difficult to carry. The head (or biting end) of the animal can be recognized by its searching movements, while the tail end is used mostly as a sucker for attachment. One can use the barrel of a 5-mL syringe to transport a leech from the container. Usually attachment occurs quickly; however, if the leech is reluctant to bite, make a small needle prick on the skin to produce a tiny droplet of blood, or try another leech. If persistent resistance to feeding occurs it is often indicative of poor arterial supply (bad sign for the treated tissue) or the presence of some residual materials on the animal's skin. To prevent leech wandering, form a barrier by cutting a 1 cm hole in the middle of a dampened gauze square and locating the hole in close contact with the area to be treated. Alternatively, a transparent, non-permeable dressing material with a hole cut into it can be used. The leech will usually stay in the same place until feeding ends, which is about 10 to 30 minutes. It is important not to disturb the leeches during feeding as this could result in premature detachment and regurgitation of the leech stomach contents into the bite wound. The bite will continue to ooze for an average of 3 to 6 hours.

Used leeches should be put in a container with the treated animal's name on it and the date of use for future therapeutic sessions on the same patient with the same leeches.

Remember, weigh the leeches after the treatment to help assess the patient's blood loss, as well as weighing the gauzes used during and after the procedure. The treated animals usually do not care much about the use of leeches since the procedure is a nonpainful one. For use in an animal's mouth to treat stomatitis or similar conditions, we do a short isoflurane anesthetic regime.

Hirudo medicinalis has an obligatory symbiotic relationship with a bacterium *Aeromonas hydrophila* (*Pseudomonas hirudinis*). The bacteria breaks RBC hemoglobin, and also secretes antibiotics to prevent other bacteria growth, as well as production of needed vitamins (as B vitamins) to the leech. The bacteria is not present in the mouth parts of the leeches, but deep in its gut. Nevertheless, if we disturb the leeches during feeding, this could result in regurgitation of the leech stomach contents into the bite wound with bacteria. If this happens, the animal should be given antibiotics (as new quinolones) for 3 days. Some veterinarians are giving the leech itself antibiotic prior to the therapy. Used leeches should not be returned to the un-fed leech container, because leeches may feed off of each other. They can be saved for re-use on the same patient, although they may not be ready for another blood meal for a month or so. Leeches that are saved for re-use must be kept in a container labeled with the patient's information and date of use. Do not dispose any live leeches into any sinks due to possible environmental contamination. Some clinicians dispose of leeches after a single use. Leeches should be disposed off by placing them in a container of 8% alcohol to narcotize them, then into 70% alcohol for 5 minutes to kill them, and then they can be disposed as for other infectious waste. In our clinic we keep them for 3 months for possible future use on the same patient; if this is not needed, we put "these hard-working animals" in a huge tank in which they can grow old and live out their entire 20 years.

Families are often repulsed by the idea of VHT. Good client education is needed. Explain to the family that leeches are an accepted medical treatment all over the country for the last few years, and approved by the FDA, with proven history of success.

PROLOTHERAPY – A GREAT CAVM METHOD TO SOLVE MUSCULOSKELTAL PROBLEMS

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Prolotherapy is defined by *Webster's Third New International Dictionary* as "the rehabilitation of incompetent structure, such as ligaments or tendons, by the induced proliferation of new cells" that is done for the purpose of strengthening weakened connective tissue and alleviating musculoskeletal pain. The term derived from the word *prolo*, short for proliferation, as the therapy is intended to proliferate tissue growth in the damaged area.

Prolotherapy is also called "proliferation therapy" and "regenerative injection therapy" (RIT).

Prolotherapy can be distinguished from sclerotherapy, the use of injections of caustics into the veins, in vascular surgery and dermatology, to remove varicose veins and other vascular irregularities.

In prolotherapy we inject solutions into the area where connective tissue has been weakened or damaged through injury or strain. Many solutions are used, including dextrose, lidocaine, a combination of both, the animal's own blood, added growth factors, phenol, glycerine, sodium morrhuate, and others.

The injection is given into joint capsules or where tendon connects to bone. Many points may require injection. The Injected solution causes the body to heal itself through the process of inflammation and repair. In the case of weakened or torn connective tissue, induced inflammation and release of growth factor at the site of injury may result in a 30% to 40% strengthening of the attachment points.

Prolotherapy treatment sessions are generally given every 2 to 6 weeks. Many patients receive treatment at less and less frequent intervals until treatments are required only every several years, if at all. Prolotherapy is often used as an alternative to an invasive and expensive surgery.

In our practice we are using 15% dextrose as our injection solution into ligaments. Added to the solution is a small amount of lidocaine without epinephrine. We take 1 mL of lidocaine 2%, 3 mL of 50% dextrose, and 6 mL of sterile water. We shave the area to be injected, scrub it with Septal Scrub (4% chlorhexidine), wash it with alcohol 70%, and finish up the preparation by putting PVP Iodine 10% on the area. The injection is done with 27- to 30-gauge needle and it is important to inject small webs into the ligaments rather than one or two large amounts. In most animals, this can be done without sedation or anesthesia. In some active animals, sedation or short-time anesthesia is needed.

For a successful therapy, one should know the anatomy of the region to be treated. We know that many acupuncture points are located at the junction of ligaments to bones, or in ligaments; therefore, it is easier to a qualified animal acupuncturist to locate the proper sites for injections, and be able to manipulate the small needles.

Usually there is some local pain and swelling for a few weeks, and great improvement is achieved after this period of time. In the first few weeks one can give nonsteroidal anti-inflammatory drugs (NSAIDs) on and off as needed, but not as a routine protocol—after all, we are looking for the inflammatory response to boost in.

Limited physical activity is advised (eg, no jumping), but the owner should be instructed to do manual therapy two to three times a day for the first few months. In some animals "a tune-up" injection is needed after 6 or 12 months.

Different solutions can be injected in prolotherapy:

- Osmotic proliferants that by their higher osmotic pressure induce the process of inflammation and healing (eg, dextrose, which is water-soluble and is not stored in the body but excreted out)
- Irritants are substances that alter the surface of the cells and induce the process (eg, phenol)
- Particulates such as pumice flour or the animal's own blood attract macrophages and induce the process of prolotherapy
- Chemotactics that directly attract immune system cells to the area (eg, sodium morrhuate)
- Growth factors

PROLOTHERAPY'S MECHANISM OF ACTION

The mechanism of action is complex and multifaceted. Six identified components include:

- The mechanical transection of cells and matrix induced by the needle, causes cellular damage, stimulating an inflammatory cascade.
- Compression of cells by the extracellular volume of the injected solution stimulates intracellular growth factors.
- Chemomodulation of collagen through inflammatory proliferative, regenerative/reparative responses is induced by the chemical properties of the proliferants and mediated by cytokines and multiple growth factors.
- Chemoneuromodulation of peripheral nociceptors and antidromic, orthodromic, sympathetic and axon reflex transmission.
- Modulation of local hemodynamics with changes in intraosseous pressure leading to the reduction of pain. Empirical observations suggest that a dextrose/lidocaine combination has a much more prolonged action than lidocaine alone.
- A temporary repetitive stabilization of the painful hypermobile joints, induced by the inflammatory response to the proliferants, provides a better environment for regeneration and repair of affected ligaments and tendons.

Injections of irritant solutions were performed in the late 1800s to repair hernias and in the early 1900s for jaw pain due to temporomandibular joint laxity. Dr. George S. Hackett, MD, developed the technique of prolotherapy in the 1940s. He claimed in his book "Ligaments and Tendons Relaxation Treated by Prolotherapy" (1958) that he cured 90% of 656 patients. At that time, he used a fatty acids mixture as an injection solution to induce inflammatory reaction. Nowadays we are using a simple dextrose solution diluted with local anesthetic such as lidocaine to achieve the same results without the possible risks (eg, shock). Dr. Hackett found that the injected tendons increased in diameter by 40% after prolotherapy, and histologic exams showed no destruction of nerves or blood vessels and no scarring, which is a chaotic matrix of collagen fibers. The ligaments and tendons produced after prolotherapy appear much the same as normal tissue, except that they are thicker, stronger, and contain fibers of varying thickness with normal histologic organization. There is an increase in collagen-producing fibroblasts, and the ligament's orientation and internal organization is linear.

Dr. Gustav A. Hemwall, MD, is one of Hackett's most famous students, beginning his studies and treatments in the 1950s and continuing until the mid 1990s. In his study of almost 10,000 cases he reported from 75% to 90% successful results, some of which were for longstanding problems that have been resistant to other treatments.

If one is wondering what might happen in years to come with complementary and alternative veterinary medicine, the following story is of interest. Dr. Everett Koop, MD, US Surgeon General, had a severe pain followed by almost a complete paralysis of his right hand during 1980. Since no therapy was able to resolve his condition, he approached Dr. Hemwall. Dr. Hemwall treated Dr. Koop by prolotherapy injections into his neck, and the medical issue was solved in a short time successfully. Dr. Koop studied more about the prolotherapy method, endorsed it, and nowadays prolotherapy is considered as subspecialty of the American Association of Orthopedic Medicine.

INDICATIONS FOR VETERINARY PROLOTHERAPY

- Chronic pain from ligaments or tendons secondary to sprains or strains
- Pain from overuse or occupational conditions (eg, dog/horse racing) known as "repetitive motion disorders"
- Chronic postural pain of the cervical, thoracic, lumbar, and lumbosacral regions.
- Painful recurrent somatic dysfunctions secondary to ligament laxity that improves temporarily with manipulation
- Painful hypermobility and subluxation at given peripheral or spinal articulation(s) or mobile segment(s) accompanied by a restricted range of motion at reciprocal segment(s)
- Thoracic and lumbar vertebral compression fractures with a wedge deformity that exert additional stress on the posterior ligamento-tendinous complex
- Recurrent painful subluxations of ribs at the costotransverse, costovertebral, and/or costosternal articulations
- Osteoarthritis of axial and peripheral joints, spondylosis, spondylolysis, and spondylolisthesis
- Painful cervical, thoracic, lumbar, lumbosacral and sacroiliac instability secondary to ligament laxity
- Intolerance to NSAIDs, steroids or opiates.
- Prolotherapy may be the treatment of choice if the patient fails to improve after physical therapy, chiropractic or osteopathic manipulations, steroid injections or radiofrequency denervation, or surgical interventions in the aforementioned conditions, or if such modalities are contraindicated.

SYNDROMES AND DIAGNOSTIC ENTITIES CAUSED BY LIGAMENT AND TENDON PATHOLOGY THAT HAVE BEEN SUCCESSFULLY TREATED WITH PROLOTHERAPY

- Cervicocranial syndrome (cervicogenic pain, secondary to ligament sprain and laxity, atlanto-axial and atlanto-occipital joint sprains, mid cervical zygoapophyseal sprains).
- Temporomandibular pain and muscle dysfunction syndrome
- Torticollis
- Cervical segmental dysfunctions
- Cervicobrachial syndrome (shoulder/neck pain)
- Hyperextension/hyperflexion injury syndromes
- Cervical, thoracic and lumbar sprain/strain syndrome
- Costochondritis/chondrosis
- Recurrent shoulder dislocations
- Lumbar instability
- Lumbar spondylolysis
- Sacroiliac joint pain
- Sacrococcygeal joint pain
- Myofascial pain syndromes
- Ankylosing spondylitis
- Shoulder, stifle, foot and ankle chronic sprain, instability, laxity of ligaments

Some examples include cruciate ligament laxity or partial rupture, patellar subluxation/luxations, stifle collateral ligament injury, tarsocrural luxations, other carpal and tarsal luxations, temporomandibular joint luxation, shoulder, elbow, carpal, and sacro-iliac luxation, and wobbler's syndrome.

CONTRAINDICATIONS

- Allergy to anesthetic or proliferant solutions or their ingredients such as dextrose, sodium morrhuate, or phenol
- Acute non-reduced subluxations or dislocations
- Acute arthritis (septic or post-traumatic with hemarthrosis)
- Acute bursitis or tendonitis
- Capsular pattern shoulder and hip designating acute arthritis accompanied by tendinitis

- Acute gout or rheumatoid arthritis
- Recent onset of a progressive neurologic deficit including but not limited to (severe intractable cephalgia, unilaterally dilated pupil, bladder dysfunction, bowel incontinence)
- Requests for a large quantity of sedation and/or narcotics before and after treatment
- Paraspinal neoplastic lesions involving the musculature and osseous structures
- Severe exacerbation of pain or lack of improvement after local anesthetic blocks
- Relative contraindications: central spinal canal, lateral recess and neural foraminal stenosis

In summary, prolotherapy is a safe and effective medical method in which mildly irritating solution is injected into ligaments, tendons, or their insertions to bones or muscles, causing a mild inflammatory response which stimulates healing. The result is a thicker, stronger, well-organized tendon/ligament, a less sensitive one, that decreases local and remote structure stresses. Over 75% to 90% of patients treated with prolotherapy get significant improvement or cure.

HOMOTOXICOLOGY – AN INTRODUCTION OF THE MODERN VETERINARY HOMEOPATHY INTO THE DAILY ACTIVITIES OF A BUSY VETERINARY CLINIC

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The young German physician, Dr. Hans-Heinrich Reckeweg, is just graduating out of the well-known human medicine college at Bonn University. The year is 1930, a hard time in Germany, economically as well as politically, but nevertheless he opens his own clinic in the capital of the country, Berlin. But more than this, he begins practicing his own medical method—Homotoxicology. He makes following declaration: "I am writing and performing something that is quite important to medicine. It will take a long time until it will be fully recognized." He began talking about the influence of environmental pollutants on his patients' health, and keep it mind—the year is just 1930, long before the 1960s when we begun our environmental awareness. During the first years he was preparing (with his family) all the remedies needed for his practice, but more and more German physicians begun using his concept, so in order to meet the increasing demands he established in 1935 a family pharmaceutical company by the name "Heel" in order to supply the needs. (Heel is an acronym of four Latin words: *herba est ex luce,* or plants come from light). This young physician, only 25 years old, facing an unstable period of his own country, somehow found a peaceful mind, the courage to establish his own medical concept, fully developing it in his own clinic and at the center of the country, attracting so many admirers, and established a pharmaceutical company to support his own agenda. As it turned out, the young Hans-Heinrich Reckeweg was a son of a well-known family, all practicing conventional medicine. His own father suffered a serious kidney disease, and was cured by a homeopath. The family then began to study homeopathy and to practice it. In homeopathy there is a great awareness for external influences as part of the daily routine of diagnostic procedures. So it was no wonder that the young Reckeweg could develop his own thinking about the influences of environmental pollutants on his patients, and enjoy his family's support for his ideas. As Reckeweg claimed, many human and animal diseases seemed to be caused by exposure to toxins, both of external and internal nature (exogenous toxins such as viruses, bacteria, fungi, heat, cold, dampness, dryness, heavy metals, fumes, etc., or endogenous toxins such as emotions, different metabolites as free radicals, urea, etc.). He termed this principle *Homotoxicology*, that is, the study of toxins on humans. The presence of such toxins was undeniable in view of the increasingly polluted environment and widespread damaging lifestyle choices. Homotoxicolgy is a branch of medicine that seeks to identify the toxins in the body, then aids the natural defense mechanisms in clearing the toxins out of the body, thereby rendering the fluids, the matrix (connective tissue), and cells free of toxic debris. Dr. Reckeweg's theory says that "the organism is a flow-system attempting to maintain the equilibrium of this flow. The biological flow can be disturbed by substances (toxins) that tend to damage the organism. The organism attempts to defend itself against this threat: this battle of the organism against toxins is the fundamental definition of a disease in homtoxicolgy. Diseases are the expressions of the organism's battle against toxins, its attempt to counteract and expel them, or the expression of an organism's efforts to compensate for toxic damage which it has sustained," and we might say Homotoxicosis = Disease.

The disease goes through a certain evolution: in the **first phase** (out of six), the toxins excreted through physiological orifices by increasing production of normal bodily fluids (as tears, saliva, mucus, sweating, urination, diarrhea, sneezing, etc). This first phase is named **"The Excretions Phase."** This is almost a normal-natural situation known to all of us, manifestations of increased physiological excretion mechanisms, as for example when someone is puffing a cigarette smoke in our face (an external toxin), or when we have a deep emotiom (an internal toxin), and we begin tearing or coughing.

The **second phase**, **"The inflammation Phase,"** is done by the body after its unsuccessful attempt to expel toxins in the first phase. The organism is aiding the inflammatory system locally or systemically to fight the toxins—for example, rhinitis, laryngitis, colitis, etc. This phase is marked by exudative inflammation. So far the fight is centered in the body fluids, so these two phases ....have a common name, **Humoral Phases**. In these clinical situations the intracellular systems are not disturbed. When the toxins can not be "burned out," they must be stocked in the connective tissue & adipose tissue (the matrix). At first, the toxins are deposited in the mesh of the extracellular matrix, as in the formation of cysts, mucous membrane polyps, prostate gland hypertrophy, lipoma, warts, kidney, bladder or gallstones, etc. The organism initializes attempts to excrete these toxins again and again, which causes symptoms to flare up. This **third phase** is named "**Deposition Phase.**" The toxins are not integrated into the structural components of the matrix, simple excretion of the toxins is possible, and up to this stage of the disease's evolution the treatment is easier, and its outcome is good to very good. In homotoxicolgy we mark the good prognosis by putting an imaginary boundary between these phases to the next phases, and we name it "**The Biological Division,"** as further on, a spontaneous endogenic excretion of the toxins is impeded.

As the toxins become an integral part of the matrix, along with changes in its structural and functional components, the body moves to the next, **fourth stage**, **"The Impregnation Phase."** This time the toxins become integral part of the matrix, they cause structural and functional changes in the matrix, more clinical signs are seen, and primordial damages to the cells in the organ occur. In this phase the disease may remain latent and later give rise to a locus minoris resistentiae, site of diminished resistance—for example, chronic rheumatoid arthritis, COPD, autoimmune diseases, asthma, IBD, etc.

Since in the third and the fourth phases the toxins are deposited in the matrix, the combined name for these two stages is "**The Matrix Phases.**" The body attempts to maintain life as long as possible, but next the toxins might penetrate the cells themselves, and in these cellular phases, the cells are increasingly destroyed. The defense system is no longer able to excrete the toxins out of the cells, or out of the matrix by virtue of its own strength, and we name this inability, "**Regulation Rigidity.**" The **fifth and the sixth phases** in these **"Cellular Phases"** are "**The Degeneration Phase"** (with serious damage and destruction of large cell groups, their enzymatic functions, and energy production systems) that is much more difficult to influence, followed by the last, the **sixth phase** in this evolution scale of diseases, "**The Dedifferenation Phase,"** or **"The Neoplastic Phase."** Diseases of this phase are characterized by the development of undifferentiated, nonspecialized cell forms. Malignant diseases stand at the end of this phase. Each one of us should try to locate any animal presented on this six-phases table as part as our diagnostic effort, in order to be able to select the proper regime of anti-homotoxic drugs, to allow us to give a prognosis for each case, and to be able to evaluate our therapeutic success or failure.

Reckeweg noticed that a disease can start in one tissue (dermatitis in the skin), and later develops in another tissue (asthma in the lungs); this shift is called *vicariation*. Vicarius comes from Latin, *vicarious* = substitute. The disease might shift as well from one phase to another, and back and forth. **Progressive vicariation** is an aggravation of the total clinical signs, and **regressive vicariation** refers to an improvement of the clinical signs. We can evaluate our success or failure by locating our patient on this scale, and see if the clinical signs are improving or deteriorating. By using this scheme one can see that the development of dermatitis into asthma is considered to be a negative process, as the disease goes deeper into the animal to an impregnation phase. On the other hand, when we treat asthma, the occurrence of skin problems is a positive sign, and should not be suppressed. These temporary signs are expected, the owner should be notified in advance that these clinical signs are needed for the healing process. The healing process itself is going from vital organs towards body's parts of less importance, from the inside towards the outside, from the top to the bottom, and in reverse chronological order (ie, the clinical signs that appeared last, disappear first).

In view of what you have read so far, we might ask: What are the objectives of anti-homotoxic therapy?

- **Prevention of illness,** and that can be achieved by toxins avoidance (eg, a change in the environmental conditions, or change in the nutrition plan provided for the animal).
- **Symptoms management**, by reversion of symptoms (regressive vicariation) and supporting forces of spontaneous healing. When performing a symptomatic approach, a veterinarian can use the western diagnosis of his/her choice for the right remedy. The therapeutic indexes of homotoxicology books can easily help out an inexperienced veterinarian in making the choice of the proper remedy.
- **Detoxification** by induction of excretion and toxins elimination (through activation of excretory organs as liver, gallbladder, kidney, gastrointestinal system, lymphatic system, skin, respiratory system, and mucus membranes). Here we are going to use drainage remedies.**Regeneration of damaged tissue by organic function strengthening, cellular function activation, and immunomodulation,** by giving an animal organ preparation with enzymatic catalysts, and a properly selected nosode to clear up the animal out of toxins that might be present in deep tissues.

The therapeutic effort must aim to activate and support body's endogenous defense mechanisms, and that should be done without compounding the problems that are caused by toxins already present (antibiotics, hormones, etc.). For example, when we give 1,000 mg of acetylsalicylic acid (mol wt 180.2) ~ 5.5 nmol or 10^{20} molecules, means that each of 10^{14} animal cells are impacted by a million molecules of the active ingredient. Homotoxicology works with the weak stimuli that are characteristic of homeopathic therapy, as explained by Drs. Rudolf Arndt and Hugo Schultz: "The strongest stimuli by a given drug in a too-large-quantity (an overdose) will suspend life's functions, a strong stimuli might inhibit the bio-system, a moderately strong stimuli will accelerate life functions, but a weak stimuli will stimulate life functions."

There is another interesting aspect in homotoxicology named "**Immunological Bystander Reaction.**" When we give an animal a homeopathic remedy at the concentrations used in homotoxicology (there are minute quantities of ingredients in the remedy), it stimulates in situ macrophages to phagocytize the remedy. The ingredients are in amounts too small to produce a complete immunological reaction. After phagocytosis, the macrophages return molecules of the ingested substances to their surface. These molecules (motifs) are bound to membrane-related Major Histocompatibilty Complexes (MHCs) on the macrophages. Nearby naïve and undifferentiated lymphocytes (Th0) recognize the motifs, remove them from the macrophage, and bind them to their own receptors. This specific action is a signal for Th0 transformation to regulatory lymphocyte (Th3), a committed lymphocyte. The Th3 cells wander into regional lymph nodes, and via cell division multiply to many "motivated and committed" cell clones. Via blood vessels, these leave the lymph nodes and reach all organs and tissues. The indicated motifs facilitate an increased penetration of the Th3 cells into the relevant area. Chemotactic factors (complement factors, chemokines, etc.) from the inflamed area support this organo/histotrophy. As soon as Th3 reaches the target organ (recognition, similarity between their motifs and the target cells organ), Th3 cells immediately start to synthesize Transforming Growth Factor-beta (TGF-beta, the body's most potent anti-inflammatory cytokine) and start inducing Th2 to release interleukin- 4 and 10, which support the effect of TGF-beta. This stops inflammatory processes and regenerates normal tissue.

ANTI-HOMOTOXIC THERAPY OBJECTIVES

- **Prevention of illness**: Toxins avoidance
- **Symptom management**: Reversion of symptoms (regressive vicariation) supporting forces of spontaneous healing
- **Detoxification**: Excretion induction Homotoxins elimination
  - Excretory organs activation (LIV/GB, KID/BL, GI, Lymph, Skin/MM, Resp)
- **Regeneration**: Organic function strengthening, Cellular function activation, Immunomodulation
  - So, as far as therapeutic steps/stages one should work
- Stage 1: Symptomatic remedy
  - [avoid toxins and symptoms management: reversion of symptoms(regressive vicariation), supporting forces of spontaneous healing]
- Stage 2: **Drainage remedy**
  - [prevention of illness by detoxification: excretion and induction of homotoxins elimination, done by excretory organs activation (LIV/GB, KID/BL, GI, Lymph, Skin/MM, Resp)]
- Stage 3: **Organ preparation/catalyst/adj allopathic medic'**_[Regeneration: Organic function strengthening,
  - Cellular function activation]
- Stage 4: **Nosode/Injeel preparation**
  - [Immunomodulation]nAdd Rx at home + Ce + evaluation

Example: K-9 Seborrhea Stage 1: **Symptomatic remedy**_- Schwef-Heel
Stage 2: **Drainage remedy -_Galium**-Heel + Cutis compositum
Stage 3: **Organ preparation/ catalyst/adj allopathic medic** Ubichinon/Hormeel/Thyreoidea compositum
Stage 4: **Nosode/Injeel preparation** Immunomodulation] Psorinoheel nAdd Rx at home + Ce + evaluation

One can combine homotoxicology with acupuncture – homeosiniatry by using 5 elements:

Rx using Sheng Cycle	In Deficiency - Tonify the Parent In Excess - Sedate the Child
Rx using the Ko Cycle	In Deficiency - Sedate the Grandparent In Excess - Tonify the Grandparent
Rx using Sheng+Ko Cycles	In Deficiency - Tonify the Parent & Sedate the Grandparent In Excess - Sedate the Child & Tonify the Grandparent

Or use the 4 (8) Needles Technique for Deficiency:

(1) Tonify the Parent point of the affected ElementTonify the Horary point of the parent Element
(3) Sedate the Grandparent point of the affected Element
(4) Sedate the Horary point of the Grandparent Element

Or use the 4 (8) Needles Technique for Excess:

(1) Sedate the Child point of the affected Element
(2) Sedate the Horary point of the Son Element
(3) Tonify the Grandparent point of the affected Element
(4) Tonify the Horary point of the Grandparent Element

HOW TO PRESCRIBE ACCORDING TO SHENG OR KO CYCLES?

A **Tonification protocol** for of a specific process on one acupoint:

(1) Pin-point the deficient Process and select a specific remedy for it;
(2) Select a relevant tonification remedy;
(3) Mix the 2 remedies at the same syringe;
(4) Select the proper acupoint to be injected;
(5) Inject.

or -

A **Sedation protocol** for a specific process on one acupoint:

(1) Pin-point the Excessive Process and select a specific remedy for it;
(2) Select a relevant Sedative remedy;
(3) Mix the 2 remedies at the same syringe;
(4) Select the proper acupoint to be injected;
(5) Inject.

Needless to say, we can combine the two prescriptions to work on the Sheng + Ko Cycles

REGARDING THE ABOVE-MENTIONED PROTOCOLS WE SHOULD NOW ASK

(1) "What is a specific remedy for the Process at hand (pin-point the Process)?"

A specific remedy exists for every Zang Fu imbalance:

LU conditions	Euphorbium Comp ad us. vet.
LI conditions	Mucosa Comp
ST conditions	Nux vomica Homaccord
SP conditions	Momordica Comp
HT conditions	Cactus Comp
SI conditions	Veratrum Homaccord
BL conditions	Cantharis Comp
KID conditions	Berberis Homaccord
PC conditions	Apis Homaccord
TH conditions	Hormeel
GB conditions	Chelidonium Homaccord
LIV conditions	Hepar Comp Heel

(Note: This is the basic list, just "the tip of the iceberg"; more accurate and specific remedies can be found in the different veterinary guides provided by the different companies.)

(2) What remedies are used to Tonify or Sedate?

To Tonify in acute cases use	Coenzyme Comp
To Tonify in chronic cases use	Ubichinon Comp
To Sedate in acute cases use	Lymphomyosot
To Sedate in chronic cases use	Galium Heel

LET US WORK ON A CASE USING THE SHENG & KO CYCLES

Q: What is the TCVM diagnosis?

A: KID Chronic Deficiency

Therapeutic Plan: Tonify Metal pt. & Sedate Earth pt = Tonify KID-07, Sedate KID-03

Q: What is the specific remedy for the specific imbalanced process (KID)?

A: Berberis Homaccord

Q: Is it acute or chronic & what remedy accordingly to be given for tonification & sedation?

A: It is a chronic condition= Ubichinon for tonification, Galium Heel for sedation

Treatment Plan: Inject KID-07 with a mixture of Berberis Homaccord + Ubichinon and KID-03 with a mixture of Berberis Homaccord + Galium Heel

LET US WORK UP A CASE ACCORDING TO THE 4 (8) NEEDLES TECHNIQUE

4 Needles protocol for LIV Excess (chronic):

- Sedate LIV-02 (Fire pt of Wood Element) - Hepar Comp Heel
- Sedate HT-08 (Fire pt of Fire Element) - Galium Heel
- Tonify LIV-04 (Metal pt of Wood Element) - Hepar Comp HeelTonify LU-08 (Metal pt of Metal Element) - Ubichinon Comp

4 Needles protocol for SP Deficiency (chronic):

- Tonify SP-02 (Fire pt of Earth Element) - Momordica Comp
- Tonify HT-08 (Fire pt of Fire Element) - Ubichinon Comp
- Sedate SP-01 (Wood pt of Earth Element) - Momordica Comp
- Sedate LIV-01 (Wood pt of Wood Element) - Galium Heel

TCM APPROACH TO CANCER — PART 1

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Traditional Chinese Veterinary Medicine (TCVM) uses five branches to treat disease: diet, herbs, acupuncture, tui-na, and qi kung. We can use all of these treatment strategies to help see patients with cancer live the best quality life possible.

Before going into the different methods used to treat cancer, it is important to mention the Shen, or mind, of our patients and their caretakers. In Chinese Medicine, the Shen encompasses the spirit and the mind. An animal with bright eyes and a happy countenance has good Shen. Shen is directly affected by the state of the Heart. In TCVM, the Heart refers to an organ system. The emotion associated with Heart is joy, and when there is a lack of joy, the Shen is depressed and the eyes lose their brightness.

Animals with cancer do not understand they have a disease. They know they don't feel good, and they know their owner is distressed and doesn't feel joy when they see them. We can encourage healing of the Shen of both patients and caretakers by reminding people to continue living. Allow the animal to continue working and performing as permissible. Go on walks and picnics and have fun. Don't allow friends and family to come over and mourn the living animal. Show people massage, acupressure, and other physical modalities to allow them to participate in the healing process. It is OK to be sad, but not OK to cease living while we are still alive.

If the Shen disturbance seems to be strictly Heart related (weak HT pulse, dreams, restless at night), Tian Wan Bu Xin Wan can be given. For depression caused by Liver Qi stagnation (purple tongue, isolation), think of Xiao Yao San or Cyperus 18 (Institute for Traditional Medicine).

Norman Cousins said the greatest tragedy of life is not death, but what dies in us while we live.

The Chinese recognize many different causes of cancer:

- Cancer arises from toxic sources, such as radiation, environmental toxins, or even some vaccinations.
- Cancer can be caused from emotional changes leading to Qi stagnation, demonstrated often in conventional medical literature, as in the case of breast cancer.
- Old injuries can lead to Blood Stasis, as seen in cases of osteosarcoma that had panosteitis of the same limb when young.
- Diet can play a role, whereby poor eating habits or poor diet choices leads to food stagnation, phlegm accumulation, and finally cancer.
- Zang-fu disharmony leads to organ deficiency, and stagnation.

One can often differentiate these patterns based on history or clinical presentation. Bone cancer can sometimes be found in animals with a history of panosteitis or trauma. A recent report found a link between bladder cancer in dogs and obesity (diet leading to phlegm accumulation), living in marshy areas with agricultural run-off (toxin invasion), and receiving monthly topical flea prevention (toxin invasion). It is also common to see various cancers in animals that have a long history of inflammatory bowel disease, vomiting, "sensitive stomachs," and suppressed skin disease (Zang-fu disharmony, leading to deficiency and stagnation).

In all of our cancer therapies, we want to get things moving. Cancer is always about a stagnation of Qi and/or Blood, where things have ground to a halt and now the body has lost control. The key point that is often forgotten is that many cancers started as a deficiency, a weakness that allowed friction and inflammation and deregulation to occur. We allopathically attack cancers with an herbal and nutriceutical arsenal meant to attack, destroy, crush, crack, and purge the tumor. This sounds like, and is, herbal chemotherapy.

Herbal chemo does have its place. When we look at aggressive, "hot" cancers that are metabolically active in a vital, strong animal, we may use powerful products and try beating the cancer cells into submission. Yet even the hottest, most excess animal will quickly deplete its essence while battling cancer, so please remember to always nurture your cancer animals with thoughtful, nourishing foods, herbs and acupuncture.

When a patient with cancer is examined, there are a wide variety of pulses ranging from slippery, choppy, wiry, full to weak, deep and thin. Tongues range from swollen, pale, wet blobs to thin, dark, red or purple strips.

Patients with osteosarcoma, hemangiosarcoma, and bladder cancer often present with excess heat and stagnation. Tongues are dark red, purple, or both, and pulses are full, bounding, choppy, and/or slippery, even postoperatively.

Some animals have patterns that appear excess and deficient; they may pant a lot or display polyuria/polydipsia (PU/PD). The tongue is usually some degree of lavender to purple, and the coating is dull. There is usually a history of low-grade chronic disease. Pulses can be fast, thready, thin and tight, often with blood deficiency as well as stagnation. The hair coat is often dull, and the nails are full, thickened, ridged or discolored. The focus is on moving and tonifying blood.

ACUPUNCTURE

Acupuncture can be an incredible tool for working with cancer. Our only contraindication is not to directly needle around a tumor. Because needles increase Qi to an area, they can accelerate tumor growth in some cases, when used locally.

Uses for acupuncture include moving Blood and Qi stasis, tonifying Qi, Yin, and Blood, transforming Phlegm and draining Damp, and clearing Heat.

Points used to activate Blood and dispense Stagnation could be SP 10, SP 6, ST 36, LV 3, BL 18, LV 2, BL 60, SP 8, LI 11, and PC 5. These points can be used whenever a solid mass is present, representing Blood Stagnation.

In an animal with concurrent weakness, focus is on ST 36, SP 6, and SP 10, as these points are also tonifying.

For an animal with concurrent heat signs, one can choose LV 2, LI 11, or BL 18.

If excess heat is present, use LI 4, LI 11m GV 14, wei jian, er jian, ST 44, LV 2, BL 17, CV 12, ST 36, ST 40, TH 5.

Choose heat-draining points to draw heat from the affected channel or system. Wei jian would be good for anal gland carcinoma, ST 44 for mouth cancer, and LI 4 for face cancer.

Acupuncture for tonification could include KI 3, SP 6, BL 23 and KI 7 for Yin and SP 6, BL 20 BL 17, LV 8, PC 6, HT 7 and SP 10 for supplementing Blood.

Use ST 36, BL 20, LI 4 and CV 4 to boost Qi.

To transform Phlegm and drain Damp, we can use ST 40, SP 9, CV 12, PC 6, SP 6 and CV 17.

Acupuncture has the most widespread reputation for helping patients with chemotherapy side effects.

- For gastrointestinal upset, we use CV 12, ST 36, or PC 6 for nausea and vomiting
- To stimulate appetite, use Shan gen
- For diarrhea, use ST 36, ST 25, BL 25, BL 28 or GV 1
- For leukopenia, inject B12 into BL 17 and needle SP 10, LI 4, LI 11, GV 14 and ST 36
- For Shen disturbance, remember to use An Shen, HT 7, BL 15 and BL 44

For animals getting chemotherapy, try to acupuncture a few days before or after chemo treatments to keep the Qi flowing and to minimize side effects.

TCM APPROACH TO CANCER — PART 2

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HERBAL THERAPIES

Use whatever knowledge is available to determine the presenting pattern. If the animal presents with polyuria/polydipsia (PU/PD) and other heat signs, determine if the cause is excess, deficiency, or drug-induced. The age of an animal is helpful in determining the strength of a formula, though some 12-year-old dogs have better Qi and Shen than a chronically ill, Jing-deficient 2-year-old dog. The former could take a stronger formula.

It is also very important to address underlying Spleen Qi deficiency or Dampness when choosing a formula. A weak Spleen cannot assimilate a strong Qi/Blood moving formula, and cannot handle a Blood tonifying formula. Spleen problems should be addressed as a priority over most other problems when treating herbally and with food therapy.

Many companions offer herbal formulas to treat cancers. If the primary function of the formula lists Blood moving or cracking, Qi moving, and Heat or Toxin clearing as the main function(s), it is probably a very powerful formula to be reserved for animals with strong constitutions. Formulas which also add herbs to tonify Blood or Qi, depending on the percentage included, may be safer for older or sicker animals. It is helpful to have some knowledge of the types of herbs used in cancer formulas so one can identify which formulas contain harsher herbs, and thus can cause more side effects. An animal with mast cell cancer or hemangiosarcoma may present with Blood deficiency in the face of Blood stagnation. Using a strong Blood mover in these deficient animals, without addressing underlying Blood or Spleen deficiencies, can cause some formulas to act like chemo and depress the bone marrow. One can also get gastrointestinal distress and lethargy.

Some animals with significant Qi deficiency can do quite well on astragalus-based formulas that tonify and also move Qi to some degree. Some will remain on these herbs alone, while others can start to add stronger formulas as their energy and vitality improve.

Use formulas specific for concurrent diseases. Most cancer animals have a history that brought them to this point, whether it was chronic urinary tract infections, chronic inflammation, inflammatory bowel disease, or dermatological disorders. These chronic patterns must be addressed, sometimes sooner, sometimes later, depending on the severity of the signs. Great improvements can often be seen in a case by adding a nourishing Yin tonic or a Liver-Gallbladder heat-draining formula.

HERBAL FORMULAS

The following are a small sampling of formulas that can be useful in treating cancers.

For Excess, Damp Heat type cancers:
- Stasis Breaker (Jing Tang Herbals)
- Chih-ko and Curcuma (ITM)

For older, weaker animals with aggressive cancer:
- Max's Formula (Jing Tang Herbals)
- Chih-ko and Curcuma (ITM)

The following are formulas for specific cancers (use with a general formula).

Brain Cancer:
- Otolith (ITM)
- Stasis in the Mansion of the Mind (Jing Tang Herbals)

Liver Cancer:
- Sparghanium (ITM) – can be used alone for geriatrics

Bladder Cancer:
- Shao Fu Zhu Yu Tang
- Long Dan Xie Gan Wan

Mast Cell Cancer:
- Xue Fu Zhu Yu Tang (patent – many sources)

Lung Cancer:
- Belamcanda (ITM) – excess pattern

Thyroid Cancer:
- Nei Xiao Luo Li Wan

Support Formulas:
- Astragalus 10+ (ITM)
- Wei Qi Booster (Jing Tang Herbals)
  - Many companies have formulas like those above that support immune function by tonifying Wei Qi, and many have Qi and Blood tonics as well. The polysaccharides in astragalus-containing formulas, as well as mushroom-based formulas, support bone marrow integrity while undergoing chemotherapy.
- Chemo Blood Support Formula (Golden Flower) – anemia, leukopenia
- Milletia 10 (ITM) – anemia, leuKopenia
- Antler 8 (ITM) – anemia
- Liu Wei Di Huang, Zhi Bai Di Huang Wan (patents) – Kidney Yin deficiency
- Tang Kuei 18 (ITM) – useful in cancer animals with concurrent Blood deficiency such as many brain cancers, some hemangiosarcomas and mast cell cases
- Ban Xia Xie Xin Tang (many sources) – gastrointestinal damp heat from chemo

DIET AND CANCER

Our final consideration is diet. There are many theories on how humans with cancer should be fed, although most veterinarians refer to the work of Greg Ogilvie, DVM, for current research findings.

Dr. Ogilvie has done extensive research on dogs with lymphosarcoma and osteosarcoma and the changes these cancers produce metabolically. Dr. Ogilvie found that dogs with these cancers had higher urinary nitrogen output, decreased protein synthesis, and increased glucose flux. Insulin resistance is common, causing adipocytes to dump fat from the body, leading to weight loss and cachexia. Carbohydrates are used preferentially by tumors and are converted to lactic acid. This lactic acid must be turned back into glucose by the liver at great expense to the body. The lactic acid also contributes, along with other cancer byproducts, to the nausea our patients feel.

The anorexia we often see can be benefited by using a wide variety of foods to prevent the animal from associating specific foods with the nausea. Meals should be small and fed at room temperature. Meals should not be repeated, despite a good appetite, lest the animal overindulge and never eat the food again.

The trend towards high protein, very low carbohydrate diets can be beneficial to some, but does not seem to be a universally advantageous diet. Carbohydrates that can and should be fed are complex, high in fiber, and of relatively low glycemic index. Grains should be soaked overnight and then cooked “low and slow” to get maximum assimilation. Whole oats, barley, quinoa, and millet have a low glycemic index and are very nutritious. Rice has a higher glycemic index and may be less desirable. Sweet potatoes have a relatively high glycemic index but are such a nutritionally valuable food, with a high fiber content and fructo-oligosaccharide content that one should feel fine feeding them. Other roots are also good nutritional choices except white potato, whose high sugar content may not be such a good bet.

All vegetables should be cooked. Animals lack the enzymes which digest the hemicellulose in plant cell walls, thereby limiting the nutritional value of the food.

Diets should be based predominantly on foods with “neutral” energetics (neither excessively hot nor cold), with smaller amounts of hotter or cooler foods added to aid the prevalent pattern. Charts and books are readily available to determine the thermal and energetic properties of different foods. In general, one can use 35% to 60% protein, 20% to 30% grains and/or roots, and 10% to 20% vegetables. Supplements should be added to balance the calcium/phosphorus ratio and to provide iodine, trace minerals, antioxidants, and essential fatty acids.

For an animal with heat signs, such as a dog with osteosarcoma with rapid, full pulses and a dark tongue, one could feed turkey as the primary protein, and add or substitute white fish to cool the diet more. Barley would drain damp heat while tonifying Spleen, and green beans would tonify Yin and Spleen. Some sweet potato could be added in small amounts to tonify Spleen and Blood if needed, or one could use yucca for its wonderful Yin-tonifying (anti-inflammatory) properties.

An animal with mast cell tumors is often Blood deficient. Animals with Blood-deficient cancers would benefit from more beef, liver a few times a week, hard-boiled eggs, or oily fish like sardines or salmon. Grains and starches could be oats or yams. Vegetables would be beets, broccoli, and dark, leafy greens. Fruits could be raisins, purple grapes, dates, or figs.

A RENAISSANCE – THE TRADITION AND SCIENCE BEHIND THE USE OF HERBS IN VETERINARY MEDICINE

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WESTERN VETERINARY HERBAL MEDICINE

Contemporary veterinary herbal medicine is both a science and a tradition. It represents the synthesis of many fields including botany, pharmacology, pharmacognosy, philosophy, history, pathology, ethnoveterinary medicine, research, clinical practice, and monograph study. In the last 50 years or so, science has provided new perspectives on the how herbs work, and several herbs have made their way into mainstream medicine, particularly in Europe. Randomized clinical trials of single herb interventions are relatively easy to undertake, and certainly in human medicine increasing numbers of studies are being published. Herbs may represent simply substitutes for drugs and these single herb studies support this approach.

Herbal medicine is more than this though. Undertaking herbal medicine as a discipline requires changing the way we think about medicine; from using drugs or herbs to relieve symptoms from a pharmacological perspective, towards using herbs to fundamentally alter the physiology of our patients towards health. Herbal medicine is thus aimed at restoring homeostasis by targeting predisposing and perpetuating causes of disease through lifestyle changes, nutrition, and individually prescribed herbal formulas (typically up to six herbs). A veterinary consultation can take 30 minutes to an hour. Thus the approach is complex and also a weakness when seeking to enhance the evidence base for its efficacy. Another problem with researching herbal medicine is that the medicine itself doesn't exert its physiological action through a single mechanism, as do many drugs. Instead the action of any herb or combination depends on complex interactions and activity of thousands of phytochemicals contained therein. This is in fact one of the key strengths of herbal medicine.

The complexity and multiple constituents found in plant tissues means that identification of active components is relatively recent (depending on advances in laboratory techniques) and is far from complete. The traditional interventions of herbal medicine have relied on crude extracts of plants from teas, decoctions, dried herbs and tinctures. There is a considerable body of science that exists on the physiological effects of isolated constituents and most of these are from animal studies. When we consider the plethora of research available from these studies, it might be true to say that more is known about herbal actions and pharmacology in "pocket pets" (mice, rats and guinea pigs—also referred to as laboratory animals) than any other domestic species. Knowing some of the key constituents in a herb and their actions, along with knowledge of its traditional use provides a basis upon which to prescribe in veterinary medicine.

So with all these limitations, why use an herb when we have well researched, established medicines for many veterinary conditions? It is important to keep in mind that where a conventional medicine is both safe and effective, it makes sense to use it. However, for many conditions, drug use isn't safe and not always effective; chronic diseases are chronic because the medicine is not restoring health (albeit relieving symptoms). And while we currently have good treatment options for patients with infections or parasite burdens, for example, we are challenged by diseases like cancer and allergic and degenerative diseases in animals. As well the rising issues of multiple drug resistance, drug residues and an increasing emergence of organic livestock production, mean that for all these reasons, the traditions of herbal medicine deserve consideration.

A LONG TRADITION OF HERBAL USE IN VETERINARY MEDICINE

The use of herbal treatments within veterinary medicine is not a new phenomenon, nor has it always been considered alternative! Ever since veterinary medicine as a discipline began in Europe in the 17th and ....18th centuries, plants have been an important part of veterinary herbal medicine. In fact many herbs were considered orthodox within the veterinary profession. These include herbs such as ginger, aloe, peppermint, cascara, senna, betel nut, calabar, catechu, kamala, fern, and others that are featured in the veterinary pharmacology texts and veterinary medical texts into the 1960s .

An interesting insight into veterinary medicine of the mid 1850s can be found in Dr. Finlay Dunn of Edinburgh Veterinary College's book *Veterinary Medicines: Their Actions and Uses.* Our veterinary forefathers (for there were no foremothers) were scientists. Perhaps they were not familiar with double-blind placebo-controlled protocols, but they were intelligent and curious and adept at experimentation, often to the detriment of their patients! From this book a summary of the plant medicines appears below (Table 1). They were well defined—the species, properties, and preparation—and much was known about their poisonous effects. Many experiments are discussed in the text, along with well observed species differences in doses and tolerances as well as poison susceptibility. For example, hemlock, a well-known poison, was well tolerated in horses, sheep, and cattle but easily caused death in dogs and cats (as experiments proved!). Herbs were rarely applied singularly, but in combinations with other herbs that augmented their toxicity or enhanced their efficacy. Contraindications were also stated.

Table 1. Summary of Medicinal Plants Outlined in Finlay Dunn's *Veterinary Medicines: Their Actions and Uses* (from the mid 1850s)

Herb	Action & Uses	Species
Aconite (*Aconitum napellus*)*	Powerful general sedative, anodyne, antispasmodic. Pneumonia, pleurisy, bronchitis. pain	Horses, cattle, dogs
Aloes (various species)	Cathartic, tonic, purgative, vermifuge. Constipation, colic, foreign bodies, febrile attacks.	Horse, cattle, sheep, swine, dogs
Anise (*Pimpinella anisum*)	Stomachic, carminative, flavoring, use with purgatives	Horse, cattle, sheep, swine, dogs
Assasoetida (*Narthex assafoetida*)	Stimulant, carminative, vermifuge, chronic coughs, chorea	Horses, cattle, dogs
Balsams of Tulu and Peru	Mildly tonic, stimulant, expectorant, vulnerary	
Belladonna (*Atropa belladonna*)*	Anodyne, antispasmodic, pupil dilation, narcotic, calmative. Tetanus, cancer pain, cystitis, performing operations on the eye	Horses, cattle, dogs.
Buckthorn (*Rhamus catharticus*)	Mildly cathartic. Distemper	Dogs, cats
Camphor (*Camphora officinalis*)*	Sedative, calmative, antispasmodic, slightly stimulant. Nervous irritability, pulmonary disease.	Horses, cattle, dogs
Caraway (*Corium carui*)	Stomachic , carminative, flavoring	
Cardamom (*Electtaria cardamomum*)	Mildly stimulant, stomachic, carminative, flavoring.	
Castor oil (*Ricinus communis*)*	Purgative, cathartic. Dysentery, enteritis, peritonitis, hernia, kidney and bladder disease	Dog, pig
Catechu (*Acacia catechu*)	Astringent, antiseptic (tannins) General atony, excess mucous discharges, flatulence. Externally	Horse, cattle, sheep, swine, dogs
Chamomile (*Anthemis nobilis*)	Stomachic, carminative (oil) mildly stimulant, tonic (tannins). Indigestion. External vulnerary	
Chinchona	Astringent, antiseptic, tonic, antiperiodic. Improves appetite, digestion, chronic diarrhea, convalescence, diabetes	Cattle, dogs, sheep, horses
Colchicum (*Colchicum autumnale*)	Cathartic, diuretic, emetic, sedative Rheumatism, ophthalmia	Horses, cattle, dogs
Croton seeds and oil (*Croton tiglium*)	Cathartic and externally counter irritant. Tetanus, constipation, congestive puerperal fever, arthritis	Horse, cattle, sheep, dogs
Digitalis (*Digitalis purpurea*)*	Topical irritant, sedative, diuretic	Horses, cattle, dogs
Euphorbium – cactus	Topical irritant	Horses, dogs, cattle
Fennel (*Foeniculum officinale*)	Stomachic, carminative, flavoring	
Gentian (*Gentiana lutea*)	Bitter, stomachic, tonic. Chronic complaints, convalescence, simple indigestion, vermifuge, jaundice	Horse, cattle, sheep, dogs
Ginger (*Zingiber officinale*)	Slightly irritant, stomachic, carminative, mildly tonic. Stimulates mucous secretions, facilitates digestion, prevents flatus. Adjunct to purgatives	Horse, cattle, sheep, dogs
Hellebore (*Helleborus niger*)*	Purgative, anthelmintic, emetic	
Hemlock (*Conium maculatum*)*	Narcotic in small animals, carmitive rheumatism, neuralgia, diuretic, externally anodyne	Horses, cattle
Henbane (*Hyoscyamus niger*)*	Anodyne, calmative, antispasmodic. Little effect on ruminants. Dilation of pupils, substitute for opium in dogs.	Dogs.

Table continues on following page

Ipecacuan (*Cephaelis ipecacuanha*)	Irritant, emetic, slightly cathartic, sedative. Little effect on horses or cattle. Emetic in dogs, laxative. Arrest febrile complaints, eye, brain, lungs.	Cats and dogs.
Jalap (*Exogonium purga*)	Irritant, cathartic. Purgative for dog and vermifuge	Dogs
Juniper (*Juniperus communis*)	Carminative, diuretic, stomachic. Prevent sheep rot. Powerful diuretic. Oil is used for skin disease.	Horse, cattle, sheep, dogs
Linseed (*Linium* sp). Flax	Oil- cathartic, emollient. Laxative, relieving irritant poisoning, colic, relieving choking, rectal and bladder soothing	Horse, cattle, sheep, dogs
Licorice root (*Glycyrrhiza glabra*)	Demulcent, emollient, flavoring	
Marshmallow (*Althea officinalis*)	Demulcent, emollient	
Mustard (*Sinapis nigra*)	Stomachic, carminative, external counter irritant. Bronchitis, pleurisy, arthritis, wounds	Horse, cattle, dogs
Myrrh	Stimulating tonic on digestion. Indigestion, mucous discharges. Externally for indolent sores and ulcerations	Horse, cattle, dogs
Nux vomica (*Stychos nux vomica*)*	Nervous stimulant esp spinal cord. Chronic paralysis, chorea, stringhalt	Horse, cattle, dogs
Oak bark (*Quercus robur*)	Astringent, tonic. Diarrhoea, dysentery. Arresting gangrene, ulcers. Uterine prolapse, rectal prolapse.	Horse, cattle, sheep, dogs
Olive oil	Laxative, emollient	
Opium (*Papaver somnifera*)	Narcotic, sedative, anodyne, stimulant, antispasmodic, diaphoretic, febrifuge, impuissant of mucous discharges. Source of morphine, codeine, narcoline, etc. Bronchitis, pneumonia, pleurisy, influenzas, asthma, diarrhea, colic, chronic vomiting, peritonitis, enteritis, tetanus, rheumatism	Horse, cattle, sheep, dogs
Peppermint (*Mentha piperita*)	Stomachic, carminative, antispasmodic, flavoring. Indigestion, flatus, griping.	Horse, cattle, dogs
Peppers (sp)	Irritant, stomachic, rubefacient. Simple indigestion, colic. External use	Horse, cattle, sheep, dogs, swine
Rhubarb (*Rheum palmatum*) sp.	Tonic, astringent, cathartic. Astringent on skin. Facilitates digestion, cathartic. Diarrhea, dysentery. Laxative.	Horse, cattle , sheep, dogs, cats
Savin (tops of *Juniperus sabina*)*	Anthelmintic	Horses, dogs
Sugar (*Saccharum officinarum*)	Demulcent, emollient, nutritive, antiseptic, laxative. Removing spots on cornea, sores.	Horse, cattle , sheep , dogs
Tobacco (*Nicotiana tabacum*)	Sedative, antispasmodic, anthelmintic, auxiliary emetic, cathartic. Colic, tympanitis, hernia (smoke clyster). Enteritis, peritonitis. Ascaridicide. Externally mange in dogs, fleas, ticks, but can be fatal as absorbed thru the skin.	
Turpentines (incl frankincense)*	Topical irritants, stimulants in indigestion, colic, general debility, laxative, anthelmintic, diuretic. Oil is used colic	Horses, cattle, dogs.
Valerian (*Valeriana officinalis*)	Antispasmodic, calmative, anthelmintic, diffusible stimulant. Acts little on horses and cattle. Epilepsy in dogs, chorea. Allyas nervous irritability	Dogs, cats
Veratum (*Veratum album*)*	Emetic, purgative, anthelmintic. Applied externally for skin parasites	Horse, cattle, dogs

* Very low safety margin.

Other medicines described in the text include: Acetic acid, alcohol, alum, ammonia, antimony, arsenic, axunge (hog's lard), calcium salts, cantharide, charcoal, chlorine, chloroform, cod liver oil, copper compounds, creosote, ergot, ether, galls (oak), gelatine, gum Arabic, honey, iodine, iron compounds, lead compounds, magnesium compounds, mercury compounds, hydrochloric acid, naptha, nitric acid, petroleum, potassium compounds, prussic acid, pyroxilic spirit, soap, silver compounds, sodium compounds, spermaceti, starch, sulfur, sulfuric acid, spirit nitre, water, wax and zinc compounds. This list and the above table represent the sum total of veterinary medicines taught at the Edinburgh Veterinary College in 1854.

Why did we stop using herbs in veterinary medicine? In the late 19th century the American Medical Association faced vigorous competition from several quarters including naturopathic medicine, eclectic medicine, physiomedicalism, herbal medicine, and homeopathic medicine. All these were also employed by veterinarians of the day. There were some 4000 medical schools offering medical degrees after as little as 2 year's study. The AMA sought to reform medical education in a strong political move, deeming any approach other than allopathic based on the sciences of the day essentially quackery. Under the AMA's Council on Medical Education they commissioned a lengthy study of medical education called the Flexner Report which was published in 1910. The Report strongly influenced both medical and veterinary education resulting in the elimination of poorer, two-year schools of both disciplines with many of the schools offering anything but allopathic medicine forced to close down. Education was standardized and strongly regulated by the AMA. Since the discovery and use of sulfa drugs, antibiotics such as penicillin, and synthetic drugs, there has been a dramatic decline in the popularity of medicinal plant use in therapy. In parallel, within a decade or two the study of herbs all but disappeared from the curriculum of Western veterinary schools. Instead, medical plants were replaced with the toxicology of weeds. Now, the pendulum has swung to the other extreme: a resurgence of interest in the study and use of medicinal plants has been taking place during the last two decades.

HERBAL MEDICINE IS STILL THE MOST WIDELY USED VETERINARY MEDICINE

Meanwhile the rest of the planet has still largely depended upon plant based medicines for animal health care for many obvious reasons. In most African countries for example, these include manpower and logistical inputs; Scarce and erratic supply of veterinary drugs and supplies; High cost of veterinary drugs and supplies; Poor communication facilities and other modern amenities; Counter-productive government policies, which do not promote the complementary utilization of orthodox and indigenous knowledge systems ; Inadequate attention to the development of ethnoveterinary medicine and other indigenous knowledge systems. In countries like India, one survey shows that about 75% of the farmers use traditional veterinary methods. The main reasons stated for turning to traditional treatment are 1) no side effects, 2) low cost, and 3) lack of modern veterinary facilities. Foot-and-mouth disease, mastitis, fever, bloat, diarrhoea and helminthiasis are the diseases most commonly treated by means of ethnoveterinary medicine in cattle, sheep and goats, the mainstay of agriculture. The main plants used in one survey were pepper, ginger, turmeric, garlic, (*Allium sativum*), and preparations made from neem (*Azadirachta indica*) and tamarind (*Tamarindus indicus*). These sort of surveys and findings offer us new approaches, new ways of using familiar plants and perhaps some solutions to the issues we face in modern Western veterinary medicine.

Traditional veterinary practices are no longer considered as inferior, unlikely to work, or backward. Currently research into ethnoveterinary practices is intense. The whole field of ethnoveterinary medicine in livestock development is considered a mine of potentially useful information for sustainable animal health management systems that can benefit the rest of the world and there is a plethora of published literature 6 on the plants that are being used successfully for infections, parasites and many other conditions. Medicinal plants are commonly available in abundance. They not only offer the local population access to safe and effective medicines for human and animal health, they are valuable for modern medicine as sources of direct therapeutic agents; as raw materials for more complex semi-synthetic chemical compounds; as models for new synthetic compounds; and finally as taxonomic markers for the discovery of new compounds. Traditional herbal medicines are not only our past but sources of future medicines!

RENAISSANCE – THE SCIENCE AND ART OF HERBAL MEDIICNE

The literature is still relatively sparse in regards to veterinary applications of herbal medicine so there is a need to consider the herbal tradition as well as human phytomedicine and science for answers. The Veterinary Botanical Medicine Association is a group of veterinarians and herbalists dedicated to developing responsible herbal practice by encouraging research, education, strengthening industry relations (the source of our "new" medicines), keeping herbal tradition alive as a valid information source, having an influence in regulatory affairs and increasing professional acceptance of herbal medicine for animals.

The central issues in veterinary herbal medicine today are safety and efficacy. The whole field of herbal medicine in the modern veterinary setting is still experimental at best. While safety of many herbs has been demonstrated (through traditional use and science) in people and laboratory animals, safety of most medicinal herbs in domestic animals is still largely unknown, though, based on experience surprisingly few adverse events have been observed. As in human herbal medicine the safety, potency, and quality of herbal products and therefore the regulation and the registration of herbal products is a daunting issue. As practitioners, we need to consider the scientific rationale for the selection (if there is one), our clinical experience, and also draw on traditional knowledge.

Following are a just a few research summaries that support the use of herbs in veterinary practice.

Ginkgo

In Germany an open clinical trial was conducted in 10 veterinary practices. Ginkgo leaf extract was administered to 42 elderly dogs (average 11.4 years) at a daily dose of 40 mg/ 10 kg body weight for 8 weeks. Geriatric behavioral disturbances (mean duration 12 months) were significantly reduced after 8 weeks of treatment; 36% of the dogs were completely free of clinical signs at the end of the study and efficacy was judged as good or very good in 79% of the dogs. The study suggested that Ginkgo leaf extract appears to be an efficacious agent that provides a safe dietary supplement for the elderly dog with age-related behavioral disturbances

Panax Ginseng

A randomized controlled clinical trial on the efficacy of ginseng on geriatric dogs was reported in Boston in 2006. This Finish study on 80 geriatric dogs were randomsied to be given 40mg of Ginseng extract plus brewers yeast and the controls were given brewers yeast alone. The ginseng dose varied between 1.7 and 4.4 mg/kg /day depending on the size of the dog. From the start of the trial to 4 weeks, changes in 6 of 7 mental outcome measures between the treatment group and the control were significantly different. And at the end of the 8 weeks both mental and physical outcomes had improved more in the Ginseng group. Deterioration in both groups was seen after treatment ended. Ginseng was shown to improve the overall wellbeing of the geriatric dogs.

Milk Thistle

In two older trials, dogs were poisoned with hepatotoxic mushroom extract and treated with silymarin or silibinin. Treatment improved liver tissue and also survival rates. In the first trial, compared with prednsiolone, cytochrome C, and penicillin, dogs receiving Milk Thistle had liver enzymes that remained nearly normal throughout the testing period, whereas those of control dogs increased dramatically. In the second trial none of the dogs treated with silibin died whereas 4 of 12 dogs in the control group died.

Echinacea

In 2003 an open multi-centered veterinary clinical trial, Echinacea was administered to 41 dogs with manifestations of chronic and seasonal upper respiratory tract infections, including pharyngitis/tonsillitis, bronchitis, and kennel cough. Each dog was at an individual stage of the disease, with various symptoms and different severity scores, at start of treatment. There was no control group. Echinacea powder (1:3) was administered with food at a dose of 1.0 g/10 kg body weight once daily for 8 weeks. Overall efficacy showed significant improvement for 92% of 39 dogs after 4 weeks of treatment and this was confirmed after 8 weeks. Efficacy was not proven in the study (since there was no control group); however, it suggested that Echinacea can be recommended as a well-tolerated alternative treatment of canine upper respiratory tract infections.

CONCLUSION

The renaissance of veterinary herbal medicine is upon us. We reach back into tradition and search for clues and we take hold of science to provide the best of both medicines. Ultimately, as veterinarians, our pharmacopeia is greatly expanded and our limitations are reduced.

References are available from the author upon request.

VETERINARY HERBAL MEDICINE: THE SCIENCE BEHIND THE TRADITION— IS THERE A SCIENTIFIC RATIONALE FOR HERB USE AND WHERE DO I FIND IT?

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WESTERN HERBAL REMEDIES – MODES OF ACTION AND EFFICACY

Medicinal plants form the basis of healthcare for more than 80% of the world's current population, and their animals! For the rest of the planet, plants are critical to pharmaceutical research and drug development, with many plant constituents providing the basis of many of our drugs. It is estimated that 25% of prescriptions written in the US contain plant-derived active ingredients and 50% of fungal products are included. An even larger percent are based on semi-synthetic or wholly synthetic ingredients originally isolated from plants

Plant medicines are different from drugs, however. A single plant can contain thousands of different bioactive phytocompounds, and when herbal medicines are combined into formulas, the final medicine can have even more. This complexity is one of the most challenging aspects of herbal medicine research today.

The use of medicinal herbs and bioactive phytochemicals and our scientific knowledge of them comprises the modern field of phytosciences. This relatively new science involves the fields of medicine, biochemistry, physiology, chemistry, toxicology, agriculture and other diverse areas. Much of the contemporary research in herbs is about trying to determine whether traditional herb uses are actually supported, and by what mechanism. While there is ample scientific evidence on many isolated phytochemicals (mainly animal studies) and their physiological effects, we still do not understand the complete activity of most herbs, nor their effects when in combination. There are also other components in medicinal herbs such as minerals, sugars, vitamins, amino acids, lipids and other pharmacologically considered "lesser important" constituents, that can support health and healing.

An important resource is Dr. Duke's Phytochemical and Ethnobotanical Database, www.ars-grin.gov/duke, which can be accessed to find out what nutritional and other constituents occur within any given herb and which herbs contain a particular constituent. Several of the most common constituent categories with research that supports their traditional and modern use include the following.

Flavonoids are found in many plants and in high levels in Hawthorn, Grapes, Elderflower and Bilberry. Flavonoids and Proanthocyanidins (which are oligomers of flavonoids.) are almost universally antioxidant, most are anti-inflammatory and anti-neoplastic, anti-allergic and they reduce capillary permeability and fragility.

Anthraquinones are red or yellow pigments found in well-known laxative herbs including *aloe vera*, senna, yellow dock, turkey rhubarb and cascara. Their laxative effects have been supported by pharmacological research and they also have anti-inflammatory action.

Coumarins are found in many plants including Lavender, Horse chestnut, Dandelion, solanaceous plants, Poppies and Sweet Clover, Parsley and Angelica. Its fermentation product dicoumarol is a potent anti-clotting agent and forms the basis of warfarin. Coumarin actions include antibacterial, spasmolytic, vasodilative and antiedema. As medical herbs, they have use as venous and lymphatic vessel tonics.

Alkaloids are derived from amino acids and tend to be bitter tasting (thus acting on the digestive system). They are precipitated by tannins, so should not be mixed together (tannins can therefore be used to treat acute alkaloid toxicity). Pyrrolizidine alkaloids as a subgroup, are important for their potential toxicity for example in Comfrey. Another group, *isoquinolone* alkaloids include berberine, hydrastine and sanguinarine found in herbs such as Barberry, Oregon Grape root, Goldenseal and Blood Root). These alkaloids have actions that include antimicrobial, antioxidant, anti-inflammatory, ionotropic and antineoplastic.

Saponins generally have a sweet taste and lather in water. They are found in herbs such as Wild yam, Panax ginseng, Astragalus, Licorice and Ivy. They tend to have steroidal molecules with the ability to modulate effects on steroidal receptors. They have demonstrated anti-inflammatory and antiviral effects. They increase mucous production in the lungs and act as expectorants and reduce cholesterol. Saponin glycosides can cause hemolysis in large amounts but when used normally are extremely safe.

Sterols and sterolins are fats, also known as phytosterols, present in all plants, fruits and vegetables and are chemically similar to cholesterol. Beta sitosterol is the major phytosterol in higher plants and Beta sitosterolin is its glycoside. Animal studies have demonstrated that phytosterols have anti-inflammatory and antipyretic, antineoplastic, glucose-lowering, and immune-modulating activity.

Tannins are generally astringent in nature due to their ability to bind protein and other molecules. They are found in many herbs including Oak bark, Black tea, Blackberry, Witchhazel, Oak galls, black tea and witchhazel. They are used as astringents for wounds, have styptic activity; anti-inflammatory and anti-ulcer action in the gastrointestinal tract and are valuable in the treatment of diarrhea.

Volatile oils are found in aromatic herbs and include the common kitchen herbs such as peppermint, lemon balm, fennel, rosemary, cardamom and cinnamon. They are variously used to stimulate digestion and reduce flatulence (carminatives) and have shown spasmolytic activity on tracheal and gastrointestinal smooth muscle; expectorant activity affecting mucociliary clearance, anti-inflammatory activity, and antiseptic activity.

Studies on single herbs or constituents support the traditional use of herbs, but this only gives a partial view of their medicinal value since traditionally herbs are used in mixtures. While knowing something about the active constituents of herbs is important, herbalists think of plants as more than the sum of their constituents and we avoid considering a researched "active constituent" as being the central reason for a plant's efficacy.

There is much more to it! In fact the art and science of herbal medicine involves a complex individualized therapeutic intervention where the actions of individual herbs are employed together in a formula to alter the underlying physiology of the patient. Herbs can be thought to work through their scientifically supported pharmacological actions, their traditional "actions", and in modern phytotherapy, a combination of these two understandings.

WHAT IS THE SCIENTIFIC PROOF OF THE EFFICACY OF WESTERN HERBAL MEDICINE?

Contrary to what many veterinarians may imagine, there are hundreds of rigorous clinical studies on herbs in the literature, essentially in human medicine, with a small and growing number in veterinary herbal medicine. But this volume of data is still small considering the multitude of herbal medicines being used worldwide with several thousand different plants being used for medicinal purposes. A recent overview included 23 systematic reviews of rigorous trials of herbal medicines. Eleven came to a positive conclusion, nine yielded promising but not convincing results, and three were negative. The relative paucity of rigorous clinical trials is mostly due to the fact that, compared with the pharmaceutical sector, the herbal industry is small and can rarely afford the considerable expense of a clinical trial.

However, numerous randomized double-blind clinical studies have been undertaken on single herb extracts since the 1980s, mainly in Germany. Meta-analyses have been undertaken on the herbs *Ginkgo biloba,* St. Johns Wort (*Hypericum perforatum*), and Saw palmetto (*Serenoa repens*) as examples. Gingko leaf extract was developed in the 1950s in Germany to treat memory loss. This use is now supported by pharmacological evidence as well as clinical trials, and more recently its use in cognitive dysfunction in dogs has also been supported

These clinical studies combined with an enormous number of laboratory studies both in vivo and in vitro on herbs and herbal extracts, explain the mechanisms of action and efficacy for a large number of herbs. There have been a surprising number of research studies performed on cats, dogs and some large animals, and thousands on rats, mice, rabbits and guinea pigs. In *Veterinary Herbal Medicine*, published in 2006, there are over 800 citations made in the Chapter "A Systems Based Approach," referencing clinical trials and in vivo and in vitro studies supporting the use of particular herbs for particular conditions. In the chapter "Herbal Medicine in Equine Practice," there are more than 70 citations; in "Phytotherapy for Dairy Cows" more than 45 citations and in "Ethnoveterinary Medicine" there are some 140 citations. These represent just some of the research base that is published and does not take into account the published research on individual herbs and their activity and pharmacological basis. There is also a body of published research in journals in France, Italy, Germany, India, China, and elsewhere in the world. The extent of the available information and quality of the information is difficult to judge due to language and access constraints.

Many of the published efficacy studies are available on Pub Med or Medline available on www.ncbi.nlm.nih.gov/entrez. Authoritative reviews of herbal efficacy can be accessed in the Cochrane reports at www.update-software.com/publications/cochrane and The European Scientific Cooperative on Phytotherapy (ESCOP) www.escop.com is an international network of scientists and physicians, who have published material submitted to the central European medicines regulatory authorities. Another database that ranks herbal efficacy according to the rigor of the studies is available on www.phytotherapy.info. Many of these studies confirm that whole plant extracts have more than a dietary supplement effect, that they can have efficacy on a particular disease and set of symptoms.

It is likely, however, that the efficacy of herbal medicine is still underrated as problems with clinical research in herbal medicine can include using doses that are much smaller than in traditional herbal medicine (Echinacea for colds is one example where research doses are much smaller than those used by herbalists) and using the same herb or herbal combination for a particular disease when the philosophy of herbal medicine is to treat the individual patient, aiming to improve overall physiology rather than to treat the disease as such.

DEVELOPING AN EVIDENCE BASE FOR VETEINARY HERBAL MEDICINE

How do we resolve the dilemma between the traditional approach to individualizing herbal medicines for animal patients and developing an evidence base? The randomized controlled trial (RCT) is considered the "gold standard in medicine in veterinary medicine. Evidence-based veterinary medicine (EBVM), focused on the double-blinded, randomized clinical trial and systematic reviews has recently been advocated for the veterinary profession. However, there are only a small number of doubled-blinded, randomized clinical trials or systematic reviews published in the veterinary medical literature, which means veterinarians may need to rely on less valid research, such as uncontrolled clinical trials, case series, case reports, or observational studies.

There are some ways in which the evidence base for veterinary herbal medicine can be advanced practically and in a clinical setting. The first are case reports that can provide observational evidence to support veterinary herbal medicine. Case reports are relatively low on the evidence base; however, they should provide both a scientific and a traditional rationale and justification for the therapeutic intervention. Auditing of chronic cases presented to a veterinary clinic, with the same diagnosis using the patient as a control (treatment with conventional medicine then treatment with herbal medicine as a complementary or alternative) might be useful, and this is certainly how veterinary herbal medicine seems to be progressing at the moment.

Another opportunity is involvement in clinical trials. The main challenge to veterinary herbalists is that herbal medicines are individualized. However, a model developed by Bensoussan et al may be valuable to consider. They randomly allocated 116 patients to receive wither a placebo, a standard Chinese medicine prescription or an individualized Chinese herbal prescription for irritable bowel syndrome. Patients were evaluated by both a gastroenterologist and a Chinese medicine practitioner at baseline and at outcome 16 weeks later. Patients on the active treatment showed improvement compared with placebo patients. Individualized and standard treatment showed no difference at the end of the study; however, follow up 14 weeks after the trial showed patients on individualized treatment maintained their improvement while those on standard treatment did not. Based on this model, a study on osteoarthritis of the knee was conducted in patients randomized to receive either Western herbal medicines, either a standard formula or individualized treatment, or placebo. Patients were given nutritional advice, joint supplements, and continued on their conventional medicines. There were clinical improvements in all groups; however, there was significant clinical improvement at outcome compared with baseline for those taking herbal medicine compared with placebo. This model could be used to investigate patient-orientated outcomes in veterinary herbal medicine, even in patients taking conventional medicines.

Examples of published research on animals, not rabbits, guinea-pigs, mice, rats and monkeys (of which there are many more), are listed in Table 1.

References are available from the author upon request.

Table 1. Published Reports on Veterinary Use of Herbal Medicines*

Herb investigated	Type of study	Researchers	Outcome
Aloe vera	Rabbits with induced frost bite Compared with pentoxifylline	Miller, 1995	Comparable to efficacy of pentoxifylline
Aloe vera	Dogs with induced foot pad wounds Compared with antibiotic cream	Swaim, 1992	Aloe stimulates early wound healing to day 7
Aloe vera	Horses with grass sickness Compared with acetylcysteine and brotizolam	Fintl, 2002	None had a beneficial effect on survival
Astragalus	Chickens infected with Eimeria tenella Chickens infected with *Mycoplasma gallisepticum* and compared with apramycin	Guo, 2004 Gou, 2004	Enhancement of cellular and humoral responses compared to controls Stimulated beneficial bacteria and reduced harmful bacteria compared with apramycin
Atractylodes	Chickens vaccinated against Newcastles disease	Ma, 2003	Serum antibody titers significantly increased compared with controls
Berberine (from Barberry)	Dogs with leishmaniasis	Ahuja, 1993	Weekly intralesional injections highly effective against cutaneous leishmaniasis
Boswellia 400mg/10kg	Prospective open multicenter clinical trials, dogs with osteoarthritis No placebo	Reichling et al, 2004	40–70% dogs symptom free
Chaste Tree	Horses with hyperadrenocorticism Clinical trial, no placebo	Self, 2003	Reduction in clinical signs
Chaste Tree	Horses with hyperadrenocorticoism Clinical trial, no placebo	Beech, 2002	No improvement
Cordyceps	Chickens as substitute for growth promoters Compared with avilamycin	Koh, 2003	Similar to avilamycin but improved bacterial population in small intestine

Table 1. Continued.

Echinacea	Pigs, compared with Mecadox control	Holden, 2002	Increased feed efficiency and growth
Echinacea	Pigs, antibody response to porcine reproductive and respiratory syndrome virus, randomized, controlled	Hermann, 2003	No difference
Echinacea	Horses, hematological parameters, double-blind placebo controlled		Increased circulating lymphocytes and neutrophils
Echinacea	dogs with chronic respiratory signs expected to persist for at least 8 weeks, multicenter open clinical trial, no placebo	Reichling, 2004	92% of the dogs had 'good' or 'very good' improvement at 4 weeks
Fenugreek	Dogs with induced diabetes	Ribes, 1986	Lowered blood and urine glucose, improved glucose tolerance
Garlic	Dogs	Dixit, 1980	Reduced cholesterol, triglycerides, phospholipids
Ginger	Dogs, cisplatin-induced vomiting	Sharma et al, 1997	Reduced vomiting, comparable to graniseton
Gingko	Dogs with cognitive dysfunction, open multicenter trial	Hielm-Bjorkman et al, 2006	Improved cognition
Guggal 25mg/kg	Dogs, laboratory study	Dixit, 1980	Lowered cholesterol and triglycerides
Lavender (oil)	Dogs with travel-induced excitement, clinical trial, cross-over controlled	Wells, 2006	Reduced symptoms
Marshmallow	Cats, induced coughing compared with prenoxdiazine, dropropizine	Nosal'ova, 1992	Inhibited cough
Milk Thistle	Chickens, amanita-induced poisoning, controlled	Tedesco et al	Hepatoprotective against aflatoxins
Milk Thistle- silymarin and silibinin	Beagles, compared with prednisolone and cytochrome C	Floersheim, 1978	Hepatoprotective against amanita-induced poisoning compared with drugs
Milk Thistle	Dogs with giardia, compared with metronidazole and combined with metronidazole	Chone, 2005	Combination with metronidazole improved rate of clearance of infection, and did not experience weight loss
Milk Thistle	Beagles, controlled	Vogel et al, 1984	Hepatoprotective
Polyporous 500mg daily (Zhi Ling San)	Cats with induced FLUTD, controlled	Buffington et al, 1994, 1997b	Decreased struvite crystalluria and hematuria
Saw palmetto	Dogs with asymptomatic benign prostatic hyperplasia, placebo controlled	Barsanti, 2000	No positive effect discerned
Schisandra	Horses, one dose 30 minutes before exercising, double-blind crossover	Hanke, 1994	Treatment group had reduced HR and RR, increased glucose and decreased lactate
Schisandra	Chickens vaccinated with Newcastle's disease Controlled, compared with Bacitracin	Ma, 2003	Serum antibody titers significantly increased compared with controls
Tea tree (oil) emulsion	Dogs with dermatitis, open multicenter trial	Fitzi, 2002	Significant improvements observed

Table 1. Continued.

Tee tree (oil) cream	Dogs with focal dermatitis, Practitioner-blinded multicenter trial	Reichling, 2004	Clinical improvement observed
Turmeric	Dogs envenomated with non-lethal doses of snake venom Compared with antivenom and flunixin	Jarcome, 2002	No difference between topical turmeric for local effects compared to antivenom (IV), both better than flunixin
Valerian	Cats, gastric lavage, study design unknown	Von Eickstedt, 1969	Significant decreases in restless, fearful and aggressive behaviors
Varuna (Crataeva)	Dogs, study design unknown	Deshpande, 1984	Significant increase in bladder tone

* Full references to published research can be found in Wynn S, Fougere B. Veterinary Herbal Medicine St. Louis, MO: Mosby/Elsevier, 2006.

HERBAL MANUFACTURE — HOW HERBAL MEDICINES ARE MADE & HOW DO I KNOW IF THE HERBS ARE SAFE TO PRESCRIBE?

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WESTERN VETERINARY HERBAL MEDICINE

A plethora of products are available on the market. Why wouldn't we simply recommend that our clients go and buy one off the health food shop shelf for their animal? Quite apart from the standard practice of prescribing according to individual needs, one of our main concerns is whether the practitioner can be confident of product quality. Is it safe? Will it be effective? This article will help you know what questions to ask to make sure you have the right medicine!

HERB VARIABILITY

Compared with well-defined synthetic drugs, herbal medicines exhibit some marked differences, namely:

- They are defined biologically rather than chemically
- The active principles are frequently unknown
- Standardization, stability, and quality control are feasible but problematic
- The availability and quality of raw materials are very variable

All these factors mean that products from different manufacturers or even the same manufacturer of the same plant species, can vary markedly in quality depending on cultivation practices. Diurnal and seasonal variations affect the chemical accumulation in both cultivated and wild plants, and depending on the plant, accumulation of chemical constituents can occur at any time during the various stages of growth. Differences in water availability, fertilizer type, season, light exposure, nutrients, period and time of collection, method of collecting, drying, packing, storage and transportation of raw material, age and part of the plant collected can greatly affect the quality and consequently the therapeutic value of herbal medicines.

The implementation of good herb agricultural and harvesting practices is the first step in quality assurance and also plays a role in preserving the natural resources of medicinal plants for sustainable use. Commercial herbal manufacturers pull herbs from two main sources: wildcrafting and cultivation. Cultivated plants are specifically grown for the trade and are the best sources of endangered or threatened herbs, although herbalists usually prefer wildcrafting since herbs are believed to have greater "vitality" and less likely to be contaminated by pesticides and chemical fertilizers. Wildcrafting, however, is not ideal since it has led to the endangerment of a number of herbs, including goldenseal and ginseng. The impact of cultivation and collection on the environment needs to be considered. Organic cultivated herbs offer a good compromise.

The best advice for minimizing the effect of variability of products on patients is to find a reputable herbal company that manufactures according to Good Manufacturing Practice (GMP) standards, and then to use those herbal products consistently, so that you get to know the medicines well. It is important to know that the herb company you choose complies with these standards, which also ensures that the right species of herb is being used, that it is being produced and stored properly, and that it is not going to be contaminated or adulterated.

GOOD MANUFACTURING PRACTICE

The manufacture of herbal medicinal products should be undertaken according to Good Manufacturing Practice (GMP), since the Code of GMP is not applied to growing, harvesting, drying or sifting of herbs, or preliminary processing of herbal oils. Quality control through GMP is the main way to achieve a high degree of consistency for a manufacturer's products. GMP will also assist in avoiding misidentification and will ensure (as much as the code of practice is adhered to) that the herbal products will be not only safe but also therapeutically potent. However, even if a company does manufacture according to GMP, quality can still vary depending on how well they adhere to the standards and also the quality of the raw ingredients.

One of the critical issues is identification of the plant species. Substitution of one herbal raw material for another can be a serious safety issue, either when it is a sub species, the wrong species (eg, Aristolochia for Stephania causing renal failure), or a less active plant part, or when a herb is contaminated with another species (eg, Digitalis in Comfrey). Herbs have been known to be contaminated with heavy metals (eg, cadmium) and also adulterated with drugs (eg, prednisolone). Any contamination could compromise the safety and efficacy of a herbal preparation. The starting materials for herb manufacture therefore require specifications for crude plant material that includes information on the source, part used, description, identification, and reports on contamination with pesticides, microbes, mould, pests or foreign matter and purity or potency.

While the source and quality of raw materials play a pivotal role in guaranteeing the quality of the product, variations in therapeutic properties and safety can still occur during manufacturing since stability of plant chemicals can also vary. Some plant constituents are heat labile and the plants containing them need to be dried at low temperatures. Also, other active principles are destroyed by enzymatic processes that continue for long periods of time after plant collection. While the final product can be tested for stability using analytical markers; it is impossible to test for all phytochemicals in the product which could degrade at different rates. These factors account for variability of markers and active constituents in herbal preparations.

Standardization

There is a general trend towards the marketing of "standardized" herbal medicines. Advances in the processes of purification, isolation, and measuring certain phytochemicals have made it possible to establish appropriate strategies for the analysis of quality and the process of standardization of herbs in order to maintain as much as possible the homogeneity of the plant extract (Table 1). Among others, gas chromatography, high-performance liquid chromatography, thin-layer chromatography, mass spectrometry, infrared-spectrometry, and ultraviolet/visible spectrometry, used alone or in combination, can be successfully used for standardization and to control the quality of both the raw material and the finished herbal products.

Herbalists have some issues with standardization, though. Plants contain many constituents and some of them are present at very low concentrations and despite these technologically advanced chemical analytical procedures, rarely do phytochemical investigations succeed in isolating and characterizing all the secondary metabolites present in the plant extract. Also, marker substances used in standardization and quality control tests may not even really account for the therapeutic action reported for the herbal products. So we may be standardizing to one constituent, which does not actually measure the quality or efficacy of the whole product.

Tinctures

Herbal products come in many forms, from fresh, dried, tableted, powdered, tinctures, creams and gels to name just a few. Herbal tinctures are used by most herbalists, since they allow tailoring for individual patients and their conditions.

Tinctures are the most commonly dispensed liquid forms of herbs; combining liquids makes formulation and prescribing easy. Benefits include:

- Alcohol based (solvent, preservative 25% to 45%), so good shelf life and excellent bioavailability
- Concentrated – small doses can be mixed in with food
- Convenient – can blend different herbs together easily

Animals hate the taste of alcohol, but the small doses mean the taste can easily be disguised. Glycetracts are often manufactured by first extracting in alcohol, reducing the alcohol, and preserving in glycerin, which produces a more palatable product, but with a shorter shelf life. Alcohol is a useful solvent and forms tinctures with nearly unlimited shelf-lives. The percentage of alcohol needed varies according to the constituents to be dissolved, and good manufacturers vary the alcohol:water ratio to reflect the ideal extract for each individual herb. Tinctures are prepared with use of the herb (the "marc") and a solvent (the "menstruum"). The concentration of a tincture is expressed as a weight:volume ratio (w:v), that is, the weight of dried herb used to the volume of menstruum/solvent added. For example, a 1:3 product means 1 gram herb in 3 mL. This makes dosing more precise. If you want your patient to receive 0.5 grams of this herbal medicine, they would need to be given 1.5 mL of the medicine.

In the industry, two main methods are used to make tinctures and fluid extracts: percolation and maceration.

Percolation

Ground dried herb is soaked in the menstruum (solvent) for several hours. The swollen plant material is then packed into a percolator, which is a tall metal or glass cylinder. More menstruum is added to cover the plant material, and this is left to macerate for 24 to 48 hours, and sometimes for weeks, depending on the herb. The tap at the bottom of the percolator is opened to allow a slow drip, and the percolate is collected in a closed container. A number of more complicated processes are used commercially to make more concentrated extracts.

Some manufacturers make very concentrated extracts by reducing the volume of liquid under partial vacuum, then diluting in another liquid. This usually involves heat; therefore, extracts made in this way are generally considered to be of inferior quality because of the potential for heat damage to some of the constituents.

Table 1. Some Popular Herbs and Their Typical Marker Substances*

Herb*	**Standard(s)**	**Category**
Asian Ginseng (*Panax ginseng*)	Ginsenosides R_{g1}/R_{b1}	M
Devil´s Claw (*Harpagophytum procumbens*)	Harpagoside, Harpagide	M
Kava Kava (*Piper methysticum*)	Kavalactones	AS, M
Milk Thistle (*Silybum marianum*)	Silybin/Silydianin	AS, M
St. John's wort (*Hypericum perforatum*)	Hyperforin, Hypericin	M
Ginkgo (*Ginkgo biloba*)	Bilobalide, Ginkgolides	M

* The marker substances are based on their use for quality control purposes and/or because they are known active compounds. M = marker AS = proven active substance.

** *National Formulary* (published by the United States Pharmacopeia, 21st edition)

Maceration

Dried herb is soaked (macerated) in the desired menstruum at room temperature for a time. The final menstruum is allowed to settle, decanted and filtered. This process is suitable for small-scale production of tinctures.

HERB SAFETY AND ADVERSE EVENTS

Once you are satisfied that you have a quality product from a good manufacturer, how do you know it is safe? Even though herbal medicines are not without some risk,[1] they could still be safer than conventional drugs, at least in humans. The World Health Organization's monitoring center collected 8,985 reports of adverse events associated with herbal medicines from 55 countries between 1968 and 1997.[2] These were associated with a variety of explanations including inadvertently using the wrong plant species, adulteration with drugs or toxic plants, contamination with heavy metals, over dosage, interactions with drugs, inappropriate self-prescribing, or inappropriate prescriptions by practitioners. Although this number may seem impressively high, it amounts to only a tiny fraction of adverse events associated with conventional drugs held in the same database.[2]

However, the relative paucity of adverse events could also be due to a relatively higher level of under reporting.[3] More conclusive evidence on the relative risks of herbal medicine versus conventional drugs is scarce. Linde et al showed that the herbal antidepressant St. John's wort was reported to have half the rate of adverse effects compared with conventional antidepressants.[4] Kava, an effective herbal anxiolytic,[5] has been banned recently in several countries because of suspected (rare) hepatotoxicity, yet preliminary data indicate that it probably is still safer than benzodiazepines.[6] Currently the relative safety of herbal medicines is not defined, but indications from the existing data, suggest that adverse events, particularly serious ones, occur less often than with prescription drugs.[7]

The use of herbal medicines and Internet sales for the prevention and treatment of a variety of illnesses in small animals has increased tremendously in recent years and it is expected that adverse events will occur. Whereas most herbal remedies, when used as directed and under the supervision of knowledgeable practitioners are safe, the potential for adverse effects or intoxications certainly exists.[8] Adverse events reported in animals include those horses testing positive for caffeine after being given products containing guarana and ginseng or ephedra, and toxicosis in dogs given similar products, toxicosis in cats and dogs with melaleuca oil and garlic as well as chamomile in cats.[9] Adverse events should be reported to www.vbma.org.

Some herbs have a very small safety margin and should not be used unless there is no other alternative (examples include herbs used in veterinary medicine in the 1800s, such as hemlock, foxglove, aconite, and others) and herbs such as comfrey, which are excellent externally but toxic internally. In addition, there is a degree of concern for potential herb drug interactions in veterinary medicine based on issues in human herbal medicine.

CONCLUSION

In order to minimize risk and maximize safety, veterinarians need to be aware of those herbs with low safety margins, and be cognizant of potential herb-drug interactions. There are a number of evidence-based resources available to assist veterinarians in the safe use of herbal remedies such as www.pubmed.org and www.naturaldatabase.com as well as Herbal Medicine Potential for Intoxication an Interaction with Conventional Drugs by Poppenger.[9] By using good quality herbs, and by prescribing the right herbs for the patient at the right doses, those herbs will be have a high safety margin and be safe to prescribe.

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ACUTE PRESCRIBING WITH HERBS FOR COMMON VETERINARY CONDITIONS — EIGHT HERBS THAT CAN HELP YOUR PATIENTS

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HERBAL MEDICINE FOR COMMON CONDITIONS

In Western Herbal Medicine, we see several schools of thought about herbal remedies. One school uses formulas that may have four to six or more herbs and most present-day herbalists take this approach. This reflects the true power of herbal medicine, which when prescribed for the individual patient, can effectively treat chronic conditions. It does this by fundamentally changing the physiology of the patient. The other approach is to use "simples," where one or two herbs are taken in larger doses. There is certainly a move towards the use of single herbs. However, this is more to do with Western Herbal Medicine following conventional medicine's approach to treatment—for example, using Echinacea's immune modulating activity for a cold, ginger's antiemetic action for nausea, or St. Johns Wort for mild depression. The availability and use of standardized extracts follows this approach and herbs are promoted for their drug-like effect in dealing with specific problems. Standardized extracts are manufactured to provide natural alternatives to the drugs used by Western medicine. And this trend is also happening in veterinary medicine—for example, *Ginkgo biloba* has recently been shown to be useful for cognitive dysfunction in dogs.

On the other hand, "singles" do lend themselves to acute prescribing, for simple conditions in otherwise healthy patients. Using single herbs is also a good training ground for beginning veterinary herbalists to learn these medicines by using them one at a time and understanding their uses and potential. They are relatively easy to integrate into practice in order to offer a "natural" alternative or complementary medicine for patients. In this article, we look at some simple uses of herbs (some of my personal favorites) and their biomedical actions and conditions for which they can be exploited. You should be able to integrate and use them safely and for a multitude of purposes.

CHAMOMILE *Matricaria recutita*

- **Parts Used:** Dried flowers
- **Energetics:** Hot, dry
- **Clinical Actions:** Carminative, spasmolytic, mild sedative, nervine, cholagogue, antiallergic, anti-inflammatory, vulnerary, bitter tonic, antimicrobial
- **Traditional Usage & Indications:** minor diarrhea, to relieve eye strain, a spasmolytic and sedative tea, wash for minor wounds, loss of appetite, gastric ulcers, teething, motion sickness, inflamed skin. The uses may seem too many to be true, but reflect the broad activity of chamomile's constituents in the body.
- **Published Research:** Inhibits both cyclo-oxygenase and lipoxygenase, anti-inflammatory, antispasmodic, beneficial in the treatment of radiation mucositis, demonstrates anxiolytic activity.
- **Potential Veterinary Indications:** Used internally, it is probably one of the best known relaxing nervines for anxiety, especially when associated with digestive issues. German Shepherds with stress-induced diarrhea respond very well. Other animals with mild diarrhea can be given chamomile by mouth or added into food. Animals can be bathed in it. It has mild antimicrobial action. Also useful as an eye wash for mild conjunctivitis or used for topical wound therapy as a spray. Use as a wash for pruritic mice and rats. It can be added to food to reduce odor in goat's milk. Inhaled as essential oil, it can relieve nasal inflammation and sinusitis.
- **Contraindications & Toxicology**: Allergy to plants of the Asteraceae (Compositae) such as ragweed, asters, and chrysanthemums. Epistaxis and subcutaneous hemorrhage have been reported in cats associated with chamomile use.
- **Preparation & Dose:** External use: compresses, baths, rinses: 15–50 grams flower/500 mL water, steep 15–30 minutes. Vapor inhalation, 1–5 drops per liter of water. Infusion for dogs 5–30 grams per cup of water, give ¼–½ cup per 10 kg divided daily by mouth or in food. Tincture (1:2) 0.5–1.5 mL per 10 kg divided dose.

TURMERIC *Curcuma longa*

- **Parts Used:** Dried rhizome
- **Energetics:** Warm, pungent
- **Clinical actions:** Anti-inflammatory, stimulant, tonic, carminative, anthelmintic, antioxidant, antiplatelet, cholagogue, hepatoprotective, anticancer, cholesterol reducing
- **Traditional Usage & Indications:** Arthritis, diarrhea, epilepsy, pain, skin diseases, acid, flatulence, or atonic dyspepsia, prevention of cardiovascular disease and cancer; arthritis, asthma, eczema, to improve GIT and liver function.

  Ethnoveterinary uses: Ulcers, ticks, castration wounds, bleeding, eye disorders and fungal diseases, diarrhea, rheumatism, worms in poultry, constipation, udder infection, swollen teats, sprains, coughs and colds in ruminants and poultry, jaundice and for swine pox.
- **Published Research:** Most research has taken place in India and has focused upon turmeric's active curcuminoids (the most well known being curcumin) and volatile oil. The curcuminoids are an important class of antioxidant and anti-inflammatory constituents and are responsible for turmeric's vibrant yellow color. In human clinical trials, the constituent curcumin has been shown as effective as NSAIDs, without the side effects. Although the mechanism of action is not fully understood, turmeric's anti-inflammatory actions are thought due

to its ability as an antioxidant to quench free radicals, hindering tissue degeneration and its ability to inhibit the arachidonic acid cascade. Turmeric has been investigated for its antibacterial, antiparasitic, choleretic, antiviral, antiplatelet, analgesic, antioxidant, anticancer, antihepatotoxic, and antitumor effects.

- **Potential Veterinary Indications:** A paste can be applied externally to sores, wounds, bruises, bites, inflamed joints, small tumors. A decoction (25 g of the bruised root to 500 mL of water) can be applied as a lotion to relieve discomfort in conjunctivitis and other eye inflammations. As a substitute for NSAIDs, turmeric can be used with or instead of NSAIDs for pain or injury. More chronic conditions include chronic anterior uveitis, as an adjunct to cancer treatment or prevention, arthritis, skin disease, liver disease.
- **Contraindications & Toxicology:** Obstruction of the biliary tract. Hypersensitivity to turmeric. **Preparation & Dose:** Powder can be mixed with water (1 teaspoon powder to one of water) as a paste for topical application. It can be added to food to tolerance (¼–1 tsp); or ground, macerated root, 1 tsp in water added to food (¼–½cup per 10 kg). Cat 50–100 mg curcumin qid, Dog 50–250 mg curcumin tid. Tincture (1:2)1.0–3.0 mL per 10 kg.

GREEN TEA *Camellia sinesis*

- **Parts Used:** young leaves
- **Energetics:** warming, drying
- **Clinical Actions:** Stimulant, antioxidant, possible antimutagen
- **Traditional Usage:** Stimulant, diuretic, astringent and to improve heart health, flatulence, promoting digestion and improving mental processes.
- **Published Research:** Green tea extracts have been used to prevent cancer including breast, stomach and skin cancer; can increase mental alertness (contains caffeine), is anti-inflammatory, antioxidative, antimutagenic, and anticarcinogenic, has been used in the treatment of childhood atopic dermatitis, may be prophylactic for arthritis, antidiarrheal
- **Indications:** Prophylaxis against cancer, stimulant, diarrhea, arthritis, atopy
- **Potential veterinary uses:** Can be made into tea and used internally and externally. As a mouth wash it can be used after dental procedures, for flushing oral surgery, oral tumors, sore throats. Can be given internally for mild diarrhea, for cancer prevention, for adjunctive cancer therapy
- Topical tea for hot spots, as a bath for atopic dermatitis and rashes
- **Contraindications & Toxicology:** Caffiene. Avoid using large amounts in cardiovascular and renal disease, thyroid hyperfunction, or anxiety. Overdose can lead to hyperacidity, gastric irritation, reduced appetite, obstipation, or diarrhea.
- **Preparation & Dose:** 1 tsp per cup of water, ¼–1 cup per 10 kg. Can be added to food, water, or syringed in mouth

BILBERRY *Vaccinium myrtillus*

- **Parts Used:** The ripe fruit and leaves
- **Energetics:** Cool, dry
- **Clinical Actions:** Vasoprotective, antioxidant, anti-inflammatory, astringent, antiedema
- **Traditional Usage & Indications:** Bladder stones, biliary disorders, scurvy, coughs, and lung disease diarrhea, dysentery and mouth and throat inflammations, to lower blood sugar in diabetes, nerve tonic for animals. Retinal damage, night blindness, capillary fragility
- **Published Research:** Anthocyanidins, protective effects in endotoxic shock, antiulcer activity, decreased plasma triglycerides and cholesterol levels, hypoglycemic, significant vasoprotective and antiedema properties
- **Potential Veterinary Indications:** PRA, nuclear sclerosis, herbal antioxidant, geriatric patients as antioxidant support. As a tea for diarrhea
- **Caution:** Antiplatelet aggregating properties
- **Preparation & Dose:** Fresh berries 5–100 g tid, tincture 1:2, 0.5–1.5 mL per 10 kg divided. Dried herb 25–300 mg/kg divided. Standardized extract (25% anthocyanidins) 2–4 mg/kg divided dose.

ECHINACEA *Echinacea purpurea, E. angustifolia*

- **Parts Used:** Aerial parts (modern preparations) or roots (original Eclectic use)
- **Energetics**: Sweet and pungent, or cooling and dry
- **Clinical Actions:** Nonspecific immune support, immune modulating, vulnerary, antimicrobial, anti-inflammatory, vulnerary, alterative, anticatarrhal.
- **Traditional Use & Indications:** Snakebite, stings and other topical uses, chewed for toothaches and mouth sores, and smoked for headache, antiseptic and alterative, treatment of fevers, respiratory infections, local infections , digestive disorders
- **Published Research**: Immune modulating, activates macrophages and increases phagocytosis by increasing WBCs. Reduce inflammation and edema, possibly by inhibiting cyclo-oxygenase and lipoxygenase, improve respiratory infection, treat colds at their onset. Antifungal effects, protects against radiation-induced damage, vulnerary. Inhibits hyaluronidase, thereby improving integrity of connective tissue barrier in wounds. Anticancer.
- **Potential Veterinary Indications:** Viral and bacterial infections, infections (acute and chronic), especially of the upper respiratory tract. As a preventative of contagious canine cough and as a treatment, Catarrhal conditions of the nose and sinus. For gingivitis. Applied externally for wounds, cuts. Food supplement for mice as an anticancer agent.
- **Contraindications & Cautions**: Allergy to members of the daisy family. Theoretically it might interfere with immune-suppressant or other immune-

modulating drugs.

- **Preparation & Dose:** It is most effective when used at first signs of infection. Tincture 1:2, 0.5–1.5 mL per 10 kg divided. Infusion 5–30 grams per cup of water ¼–½ cup per 10 kg divided. Dried herb 25–300 mg/kg divided

MARSHMALLOW *Althaea officinalis*

- **Parts Used:** Dried roots
- **Energetics:** Sweet
- **Clinical Actions:** Demulcent, emollient, expectorant, diuretic, mucilage, anti-inflammatory
- **Traditional Usage & Indications:** Demulcent for coughs and irritations of oral and pharyngeal mucosa ,emollient for wounds and dry skin, to mask the bitter or pungent taste of other drugs, for asthma, cystitis, dysentery and irritations of the gastric mucosa. All inflammatory disorders of the GIT, respiratory and urinary tract. Externally the leaf can be used to draw abscesses out, and as an emollient for ulcers
- **Published Research**: Anti-inflammatory activity, antitussive, antimicrobial against *Pseudomonas* and *Proteus* sp. when used topically
- **Potential Veterinary Indications:** Post extubation, contagious canine cough, geriatric conditions where mucous membranes are inflamed. Acute respiratory disease, gastroenteritis, cystitis, wounds, skin ulcers, abscesses
- **Preparation & Dosage:** Dried leaf 5–30 grams in 1 cup water, ¼–½ per 10 kg divided. Glycetract 1:2, 0.5–1.5mL per 10 kg divided

MILK THISTLE *Silybum marianum*

- **Parts Used:** Seed.
- **Energetics**: Controversial, sweet and cooling & bitter, warm
- **Clinical Actions:** Hepatoprotective, demulcent, cholagogue, galactagogue, antioxidant
- **Traditional Usage & Indications:** Liver disease, splenic or hepatic congestion, to increase lactation; liver disease due to toxins; inflammatory liver disorders; cirrhosis. In cattle, milk thistle may be appropriate in the treatment of ketosis, increasing milk yield and decreasing ketonuria
- **Published Research:** Silymarin is a bioflavonoid complex. Silibinin is thought most active and probably responsible for the benefits attributed to silymarin. It decreases aminotransferase activity, silybin reduces oxidative damage to kidney cells, silybin prevented cisplatin induced nephrotoxicity in rats, but did not prevent cyclosporine-induced glomerular damage except for lipid peroxidation; may inhibit hepatic synthesis of cholesterol and reduce blood lipids; silymarin can protect the pancreas against certain forms of damage.

  Acts as an antioxidant; it inhibits lipid peroxidation in hepatocyte plasma membranes, thereby protecting against many toxins; it protects against genomic injury by suppression of lipoxygenase, hydrogen peroxide and superoxide; It increases hepatocyte protein synthesis; It stabilizes mast cells and decrease the activity of tumor promoters
- **Potential Veterinary Indications:** Because milk thistle is proven to be a liver herb doesn't mean that it's only a liver herb. Consider it for conditions affecting the spleen, pancreas, liver and kidneys, for subclinical elevations in liver enzymes or mild elevations in renal measures; as an adjunct to potentially hepatotoxic drugs and pre and post anesthesia. Hematuria is also another indication based on traditional use. Consider use in elevated triglcyerides or cholesterol. Giardia in dogs or metronidazole administration.
- **Contraindications & Cautions**: Allergies reported, Milk thistle reduces activity of CYP3A4 and UGT1A6/9 liver enzymes, and may decrease insulin requirements in some diabetics
- **Preparation & Dosage**: Flavonolignans are not very water soluble, so liquid extracts must be alcohol based. In modern phytotherapy a solid extract of the seeds is used, standardized to 70% silymarin content. Milk thistle should be used for at least 8 weeks before expecting results such as improvement in biochemistries. Dried herb 50–100 mg/kg divided, unprocessed seed triple dose. Glycetract 1–2 mL/10 kg divided, dry standardized extract (70% silymarin) 10–15 mg/kg divided

GINGER *Zingiber officinale*

- **Parts Used:** Dried rhizome
- **Energetics:** Hot, dry
- **Clinical Actions:** Stimulant, carminative, antispasmodic, bitter, anti-inflammatory, antiplatelet, diaphoretic
- **Traditional Usage & Indications:** Headaches, nausea, rheumatism and colds. To treat cold extremities, improve a weak and tardy pulse, address a pale complexion and strengthen the body after blood loss, treatment of dyspepsia, flatulence, colic, vomiting, diarrhea, spasms and other stomach complaints. To treat colds and flu, to stimulate the appetite, as a narcotic antagonist and as an anti-inflammatory agent in the treatment of migraine headache and rheumatic and muscular disorders
- **Published Research** Cholagogic activity, hyperlipidemic activity, anti-atherogenic activity, gastrointestinal activity, gingerols are reported to have antiserotoninergic activity and it has been suggested that the effects of ginger on gastrointestinal motility may be due to this; antiemetic activity (peripheral) a direct effect on the gastrointestinal tract by increasing gastric motility and adsorption of toxins and acids , anti-inflammatory activity, cholesterol-lowering, antithrombotic , as effective as ascorbic acid as an antioxidant, inhibits the activities of cyclo-oxygenase and lipoxygenase, for rheumatic pain and chronic lower back pain; gingerols inhibit the growth of *H. pylori;* antidiabetic activity (increase in insulin levels and a decrease in fasting glucose levels in diabetic

rats).

- **Potential Veterinary Indications:** Nausea, travel nausea, chemotherapy nausea, improving circulation in geriatric animals. As an adjunct for arthritis treatment
- **Contraindications & Cautions:** May affect bleeding times, stop 1 week prior to surgery
- **Preparation notes:** Infusion 5 g per 1 cup water, ¼–½ cup per 10 kg divided. 15–200 mg/kg divided of dry powder; Tincture 1:2, 0.25–0.5 mL per 10 kg divided. For travel nausea 30 minutes prior to travel 25–50 mg/kg divided.

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HERB–DRUG INTERACTIONS — WHAT YOUR CLIENTS ARE USING AND WHAT YOU NEED TO KNOW

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THE POTENTIAL FOR VETERINARY HERB–DRUG INTERACTIONS

Numerous Web sites and human practitioners are offering products for animal use. While herbal medicine is safe when used appropriately, as more animals are treated with herbs it becomes more likely that we will see herbs interacting with veterinary medications or procedures. Whether these will be clinically relevant, remains to be seen, however they should not be ignored. With some 20% of pet parents using some form of complementary medicine, the concerns are amplified when they self-prescribe for their pets. Asking what they are using should become a normal part of a history, particularly if planning surgery or initiating drug treatment. It's also important to report any suspected interactions, whether positive or negative, so that we can develop a body of veterinary-specific knowledge. This article focuses on potential herb–drug interactions that veterinarians should be aware of.

REPORTED HERB–DRUG INTERACTIONS

There are some very serious herb–drug interactions, as opposed to toxicities, reported in the human literature, especially involving St. Johns Wort and warfarin among others. However, the issue of herb–drug interactions has perhaps been largely over emphasised. One of the major problems has been that until recently the few sources of information about herb–drug interactions distinguished between interactions that were suspected and those that were well documented. Many herb–drug interactions are postulated based on potential pharmacological interactions due to a constituent in the herb, while the actual clinical relevance has not been established. Others interactions include anecdotal reports without essential data to establish a firm cause–effect relationship.

In one review to consolidate the clinical and pharmacologic aspects of drug–herb interactions, data bases were searched from 1966 to 2002. Of 162 citations identified, only 22 citations met the inclusion criteria of being adequately reported. Using a matrix of 165 possible drug–herb interaction pairs (15 therapeutic drug classes by 11 herbal products), the study identified 51 (31%) interactions discussed in the literature. Twenty-two of these 51 drug–herb pairs (43%) were supported by randomized clinical trials, case-control studies, cohort studies, case series, or case studies. The remaining interaction pairs reflected theoretic reasoning in the absence of clinical data. Most interactions were pharmacokinetic, with most actually or theoretically affecting the metabolism of the affected product by way of the cytochrome P450 enzymes. In this review, warfarin was the most common drug and St. John's Wort was the most common herbal product reported in drug-herb interactions.[1] St. Johns Wort is probably the most comprehensively investigated herb for possible interactions with anticonvulsants, digoxin, cyclosporine, theophylline, and other drugs in human medicine.

Several references can be consulted on herb–drug interactions including Poppenger's *Herbal Medicine: Potential for Intoxication and Interactions with Conventional Drugs*,[2] McGuffin et al's *Botanical Safety Handbook*,[3] Brinker's *Herb Contraindications and Drug interactions*,[4] European Scientific Cooperative on Phytotherapy (ESCOP),[5] and the German Commission E monographs.[6] Interestingly, of the more than 600 herbs mentioned by all these resources, only a relatively small number of herbs are implicated in a negative way and most of these are theoretical or speculative concerns. There are also Web sites that can provide up to date information including www.naturaldatabase.com, www.healthnotes.com, www.ncbi.nlm.nih.gov/PubMed.

Veterinary-related suspected herb–drug interactions or adverse events can be reported on the Web site of the Veterinary Botanical Medicine Association www.vbma.org. Reports should include adequate patient history; complete chronology; concurrent diseases, conditions or medications presumably not associated with the adverse event; concurrent medications, diet and supplements; adequate description of interactors; exclusion of obvious explanations other than herb–drug interaction; reasonable time sequence of drug administration to adverse event; cessation of event on stopping the drug or herb; recurrence of event with challenge.

No doubt, however, there are many instances that occur and go unreported. Nonetheless, in this author's experience of daily veterinary herbal practice, herb–drug interactions have not been detrimental. On the other hand, they have been beneficial to the patient in being able to modify potential side effects (using liver-protective herbs, for example), or reducing the dose rates of conventional medications needed, or being able to discontinue medications altogether.

CATEGORIES OF HERB–DRUG INTERACTIONS

It is beyond the scope of this article to discuss in detail the mechanisms of herb–drug interactions. However, they may be broadly classified as:

Pharmaceutical - When compounds interact due to physical or chemical interaction, such as tannins and alkaline drugs.

Pharmacokinetic - Modulation of drug absorption due to altered absorption, distribution, metabolism, or elimination.

Pharmacodynamic – Synergistic, whereby the herbal product potentiates the action of the conventional drug, Antagonistic, whereby the herb may directly antagonize the actions of the drug or a new effect from the combination not anticipated from either alone. The potential for these interactions can to some extent be predicted by knowing the constituents and pharmacology of the herb and the concurrent drug. Many lists of herb–drug interactions have been proposed based on the assumptions of potential pharmacodynamic herb–drug interactions. However, inclusion in such lists does not mean that a clinically important interaction will necessarily occur.

Several authors have further classified herb–drug interactions.[4,7,8,9] Like conventional drugs, the pharmacokinetics of herbs are influenced by factors such as species, age, and disease/health state, and hence there is potential for drug–herb interactions as well as herb–disease interactions. Oftentimes these interactions result in a beneficial reaction. In fact, one of the fundamental tenets of herbal medicine is that interactions occur between the constituents within a single plant, and between herbs in a formula, either to increase desired effects or to reduce unwanted effects or both, but this is not the focus of this article.

PRACTICAL HERB–DRUG CONSIDERATIONS IN VETERINARY PRACTICE

Concerning the potential for interactions, it is also important to consider the variability that exists in products containing the same herbal ingredient, as well as the quality of its manufacture and the dose rates. Being able to quickly calculate the herb dose is an important skill, especially since many pet parents use human products.

Proactive management to reduce the negative consequences of herb–drug interactions or to gain the positive benefits of the same, including having a knowledge of the herb's activity to predict potential issues. Understanding the herb's main constituents, actions and uses is helpful. If there are concerns, separating drugs and herbs by half to one hour or more might be worthwhile. If an owner has an animal on a drug regime and wants to introduce herbs, suggest starting with a low dose and working up slowly.

Preoperative Concerns

The need to discontinue herbs prior to surgery or anesthesia has been proposed based on the potential for herb–drug interactions prior to, during, or after surgery. The minimum period that herbs should be discontinued is unknown; however, a week, if available, seems reasonable. We utilize Milk thistle routinely in the preoperative and postoperative period for our patients to protect against the oxidative stress of general anesthesia. Other helpful herb groups include antimicrobial herbs (eg, goldenseal); antiemetics (eg, ginger); anti-inflammatories (eg, devil's claw, licorice); immune-supporting herbs (eg, echinacea); and tonics (eg, withania). Herbs to avoid in the week before surgery include those which reduce blood-clotting. Potential Increased bleeding can occur with garlic, ginkgo, ginger, dong guai, saw palmetto, and Asian ginseng. We also stop fish oils, vitamin E, and chondroitin. The sedative effect of anesthetics or sedatives can be potentially increased by kava, valerian, ginkgo, goldenseal, and St. Johns Wort. These are often stopped 1 week prior to surgery in humans.

Interference with Diagnostic Tests

While not strictly an herb–drug interaction, some herbs can influence the results of biochemistry or diagnostic tests. For example, human patients taking Siberian ginseng (Eleuthero) have elevated digoxin levels (possibly due to interference with the assay). Bugleweed (*Lycopus europaeus*) in cats can interfere with diagnostic procedures involving radioactive isotopes (author's personal experience).

Patients on Drugs with Narrow Therapeutic Windows

Patients on digitalis, anticoagulants, hypoglycemic agents, and immune suppressants such as cyclosporine should be monitored very closely if herbs are given concurrently.

Patients that are on antiseizure medications, sedatives, tricyclic antidepressants, or anxiolytic drugs along with sedative or nervine herbs need to be monitored and possibly reduced. We have certainly experienced this in our practice.

Many herbs can lower blood glucose, this is primary importance in diabetic animals and they need to be monitored closely; these include aloe, gymnema (*Gymnema sylvestre)*, fenugreek, ginseng, and bitter melon.

Likewise, patients on conventional polypharmacy are at greater risk for interaction in any number of ways, and if they are geriatric, even more so. Take care.

Patients with Compromised Hepatic or Renal Function

Patients on drugs and herbs need to be monitored very carefully. In the author's opinion herbal medicines can greatly improve the biochemical parameters and general health of these patients when prescribed appropriately.

Common Herbs that can Affect Absorption and Metabolism of Drugs

Herb constituents such as fibers and mucilages can reduce gastrointestinal absorption of drugs; examples include flax seed, marshmallow, and slippery elm. Similarly, high tannin-containing herbs such as agrimony can reduce the absorption of alkaline drugs.

Laxative herbs such as aloe *(Aloe* spp.), buckthorn *(Rhamnus frangula)*, cascara sagrada *(Rhamnus purshiana)*, and rhubarb *(Rheum* spp.) could potentially reduce absorption because of reduced gut transit time.

Licorice can increase the risk for potassium depletion when used with diuretics or corticosteroids.

Echinacea, gingko, garlic, licorice, milk thistle, and valerian are metabolized by cytochrome P450 enzymes and can influence metabolism of glucocorticoids, phenobarbital, ketaconazole, midazolam, and calcium channel blockers.

Uva ursi or bearberry leaf *(Arctostaphylos uva-ursi)* should not be administered with any substances that cause acidic urine, such as ascorbic acid and ammonium chloride, as it will reduce the antibacterial effect.

Ginger, cayenne, black pepper, and prickly ash can increase bioavailability of drugs.

Herbs that Can Protect Against Adverse Side Effects of Drugs

1. Several herbs can protect against the adverse effects of drugs on stomach and liver, including licorice, milk thistle *(Silybum marianum)*, bupleurum, and ginger *(Zingiber officinale)*. Milk thistle reduces liver enzymes in dogs on phenobarbitone (personal experience).
2. Milk thistle decreases hepatotoxicity of drugs such as halothane and phenytoin, and nephrotoxicity of anesthetics, cisplatin, and doxirubicin without reducing activity.
3. Several herbs can lower the required amount of conventional drug needed because of similar action such as licorice and prednisolone, hawthorn, and cardiovascular drugs (Hawthorn can increase the effects of cardiac glycosides while protecting against harmful effects), nettle leaf and antihistamines, astragalus and chemotherapeutics.

Basic Guidelines to Minimize Potential for Herb–Drug Interactions

Like any conventional medicine, the use of medicinal herbs must be monitored carefully. Herbs can be combined with conventional medicines but must be monitored as the dose rate required for medicines can change. Obtain herbal products from companies that have good quality control measures so that consistency is more likely. Aim to use a dosing strategy that is consistent so that you get experience with efficacy, safety, and interaction with drugs.

CONCLUSION

As part of the patient intake, ask pet parents what they might be using on their animals. It is particularly important for patients about to undergo surgery but also for patients that are diabetics, on cardiovascular drugs, anxiolytic drugs, and patients with epilepsy or gastrointestinal disease. Most herb–drug interactions are only a potential; however, it is important to monitor medicines carefully, and to report suspected interactions- both negative and positive! If you are inexperienced with herbal medicine and would like some help, contact www.vbma.org.

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HERBAL MEDICINE IN PRACTICE — DISEASE MANAGEMENT WITH ANTIOXIDANT HERBS

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In recent years there has been an increased understanding of the importance of oxidative damage in both the pathophysiology of disease and the aging process in all species. This review will describe several herbs with antioxidant activity and where they are most likely to have therapeutic activity as antioxidants in the prevention and treatment of common veterinary conditions.

BACKGROUND

A free radical is any atom or molecule that contains one or more unpaired electrons. The simplest free radical is an atom of the element hydrogen; however, there many others including superoxide, hydroxyl, thiyol, and peroxyl. Singlet oxygen is also a contributor to oxidative stress, even though it is not a free radical, so the phrase "reactive oxygen species" (ROS) is often used to encompass all the species capable of causing oxidative damage. ROS are produced naturally in as a consequence of metabolism as well as pathological processes. New evidence is emerging to suggest that the ROS can act as signalling molecules in the regulation of gene expression, cell growth and cell death.

In situations where the generation of oxidative species is increased, antioxidant defenses may be insufficient to cope, and the result is oxidative stress. Oxidative stress represents an imbalance between oxidants and antioxidants in favor of oxidants. It results in damage to lipids (eg, phospholipid membranes) via lipid peroxidation, nucleic acids (eg, leading to carcinogenesis), and proteins damage. While the inherent biological array of mechanisms to prevent oxidative damage is impressive, it can be overwhelmed. As well as the ROS generated in everyday life other factors can increase the radical species which have the potential to attack cellular components. These factors include exercise, inflammation, environmental pollution, UV light, certain drugs, anesthetics, and radiation. For example, studies carried out in racing greyhounds and sled dogs has shown that they undergo oxidative stress with exercise. Oxidative stress has also been shown to occur in normal healthy adult dogs after about 20 minutes of exercise and research has demonstrated that oxidative stress is also induced by the administration of general anesthetics and sedation in dogs.

Oxidative stress and damage to cells, especially to genetic material (DNA), is thought to be a major factor in the development of chronic diseases, aging and age related diseases including cataracts and cancer. There is a well-documented association in humans between oxidative damage and diseases like diabetes, chronic renal failure, hepatitis, colitis, allergic skin disease, arthritis, cancer, atherosclerosis, arteriosclerosis, rheumatoid arthritis, cataract formation, age-related macular degeneration, central-nervous diseases including Parkinson's disease and Alzheimer's disease and asthma. In animals, an association between free radical generation and pathophysiology has been demonstrated in many conditions including:

- Inflammatory skin disease in dogs
- Immune-mediated hemolytic anemia (IMHA) in dogs
- Periodontitis in dogs
- Heat stress in dairy cattle
- Transport stress mortality in beef cattle
- Leishmaniasis in dogs
- Cataracts in poodles
- Gastrointestinal tract (GIT) ischemic injury in horses
- Canine chronic hepatitis
- Senile dementia in dogs
- Chronic inflammatory airway diseases including heaves in horses

Cats are uniquely sensitive to oxidative injury to erythrocytes, and Heinz body formation, as the result of exogenous oxidant exposure as well as endogenous disease processes such as lymphoma, diabetes mellitus, and hyperthyroidism.

Antioxidants (also called free radical scavengers) are therefore the major defense against oxidative stress. They are produced within the body and include enzymatic scavengers such as superoxide dismutase (SOD), catalase, glutathione peroxidase; enzymes such as glutathione (GSH) reductase; hydrophilic radical scavengers such as ascorbate, urate, and glutathione; hydrophobic radical scavengers such as tocopherols, flavonoids and carotenoids; the cellular biochemistry that maintains a reducing environment (eg, glucose-6-phosphate dehydrogenase) and the storage and transport of copper and iron ions in forms that prevents formation of free radicals. In addition to these, antioxidants include minerals (eg, selenium), vitamins (eg, C and E), and phytochemicals such as flavonoids, proanthocyanidins, polyphenols, lignans, and other carotenoids. Most antioxidant compounds in plants are polyphenolic and since most plant parts contain polyphenols, most herbs will have antioxidant activity.

Camellia sinensis

Green tea polyphenols (GTP) decrease lipid peroxidation in skin and protect against lipid peroxidation. GTP also scavenges singlet oxygen. GTP in mice increased antioxidant and glutathione peroxidase, catalase, and quinine reductase in skin, small bowel, liver, and lungs. The combined activities make green tea an effective chemopreventive agent against the initiation, promotion, and progression stages of multistage carcinogenesis.

Polyphenolic compounds (catechins) found in green tea were investigated on bovine and human cartilage cultured with and without reagents known to accelerate cartilage matrix breakdown. Catechins were effective at inhibiting proteoglycan and type II collagen breakdown and it was concluded that some green tea catechins are chondroprotective and that consumption of green tea may be prophylactic for arthritis and may benefit the arthritis patient by reducing inflammation and slowing cartilage breakdown.

Green tea consumption decreased oxidative DNA damage, lipid peroxidation, and free radical generation in smokers. Non-smokers also exhibited a decrease in overall oxidative stress.

Potential veterinary uses include:

- Prophylaxis and treatment of cancer, arthritis, atopy, periodontal disease.
- Prophylaxis in animals living in smoking households

Vitis vinifera

Red wines contain a variety of polyphenolic antioxidants. The total antioxidant activity of wines investigated was well correlated with phenol content and polyphenols are, in vitro, significant antioxidants. Procyanidolic oligomers (OPCs) from pine bark and grape seed demonstrated the strongest free radical scavenging activity when compared with citrus flavinoids and other flavinoids.

Resveratrol, a phytoalexin found in red wine, in fact inhibits the metabolic activation of carcinogens, has antioxidant and anti-inflammatory properties, decreases cell proliferation, and induces apoptosis.

The anticataract activity of a grape seed extract (GSE, which contains 38.5% procyanidins) was investigated in hereditary cataractous rats. The results suggested that procyanidins and their antioxidative metabolites prevented the progression of cataract formation by their antioxidative action. Many proteases participate in various ocular pathologies and no really effective treatments are currently available. Procyanidolic oligomers (PCO) from grape seeds have demonstrated protection against proteolytic attack, for the bovine cornea in vitro.

Semen of different ejaculates collected from breeding rams was mixed with various antioxidants including resveratrol. A significantly higher proportion of motile sperm cells was observed in the treated than in the control samples. The frequency of acrosomal defects was lower in the treated groups than in the control. Antioxidants including resveratrol can improve the effects of ram semen preservation.

Oral administration of bioflavonoid antioxidants (containing grape seed extract) to cats at risk for oxidative stress may have a beneficial effect on their ability to resist oxidative injury to erythrocytes.

Potential veterinary uses include:

- Feline leukemia viral infections, feline lower urinary tract disease (obstructed)
- Bovine corneal disorders, various ocular pathologies including retinopathies, antioxidant support for geriatric animals or those with cardiovascular disorders, photosensitization and prevention of sunburn in depigmented animals, antiinflammatory support, prevention of postoperative edema, sports injury edema, treatment of early cataracts and nuclear sclerosis, systemic mast cell tumor

Crataegus (Hawthorn)

Crataegus contains OPCs, so much of what is known about grape seed extract applies to Crataegus. Hawthorn also contains flavonoids and phenolic acids with antioxidant activity. Hawthorn tincture inhibited the oxidation of LDL and VLDL in diabetic patients and provided a protective effect in atherosclerotic rats. Antioxidant enzyme levels were normalised in the liver, aorta and heart tissue. Crataegus has been shown to increase SOD activity in red blood cells in vivo after oral doses.

Potential veterinary uses: Antioxidant support in cardiovascular disease, oxidative stress, capillary disorders, edema, red blood cell disorders such as autoimmune hemolytic anaemia

Silybum marianum (Milk Thistle)

Silymarin decreases lipid peroxidation in hepatocyte plasma membranes, thereby protecting against many toxins. It also suppresses lipoxygenase, hydrogen peroxide, and superoxide. It increases the levels of glutathione in the liver, intestine and stomach and increases SOD activity in red blood cells and lymphocytes. Silybin reduces oxidative damage to kidney cells in vitro. As an antioxidant, silymarin can protect the pancreas against certain forms of damage. Plasma total antioxidant capacity was significantly increased in volunteers taking 858 mg/day silymarin compared with placebo.

Potential veterinary uses: Hepatitis, nephritis, pancreatitis, cholangiohepatitis, toxic injury to liver, hepatic lipidosis

Curcuma longa (Turmeric)

Curcuma inhibits lipid peroxidation in liver and brain tissue; it inhibits hydrogen peroxide and nitrogen generation from macrophages in vivo; reversed alflatoxin induced liver damage in vivo (presumably via antioxidant action and inhibited iron induced lipid peroxidation in the rat liver. Glutathione peroxidase, SOD and catalase levels were also raised, suggesting curcumin inhibits lipid peroxidation by raising antioxidant enzymes.

Potential veterinary uses: Prevention of cardiovascular disease and cancer; arthritis, asthma, eczema, to improve GIT and liver function, chronic anterior uveitis, adjunct cancer treatment.

Salvia miltiorrhiza (Dan Shen)

Dan Shen is a potent antioxidant with free radical scavenging activity and has been used as antioxidant therapy in heart-lung bypass surgery to reduce myocardial damage and attenuate postoperative vasoactive mediator imbalance. It protects rat hepatocytes against carbon tetrachloride (CCl4)-induced necrosis.

Potential veterinary uses: Impaired peripheral and cerebrovascular circulation, acute and chronic liver disease, promotion of healing of fractures and other injuries, nerve compression, as an adjunct to treatment of lymphoma, autoimmune disease, recovery from cerebrovascular accidents

Vaccinium myrtillus

Phenolic compounds (anthocyanosides) in bilberry inhibit protein and lipid oxidation, bilberry has a particular affinity for the eyes. Anthocyanoside concentration in the fresh fruit is approximately 0.1–0.25%, while concentrated bilberry extracts are usually standardized to 25% anthocyanosides.

Potential veterinary uses: Progressive retinal atrophy (PRA), nuclear sclerosis, capillary fragility, geriatric patients

Schisandra chinensis

Schisandra lignans act as free radical scavengers and inhibit iron-induced lipid peroxidation (including brain cell mitochondria and membranes) and superoxide anion production; they increase SOD and catalase levels in the liver in vivo.

In a randomized, double-blind, cross-over study, 18 healthy horses received a single dose of *Schisandra* concentrate (equivalent to about 50 g of dried berries, containing 1.2% schisandrins) or placebo 30 minutes before a test race. For the race horses, the exercise consisted of an 8-minute race over 5.6 km. The show-jump horses were taken over a 700 m obstacle course with 12 jumps. Treatment with *Schisandra* reduced heart rate and respiratory frequency, increased plasma glucose,and decreased lactate levels in both exercise groups, although the effects were more marked in the race horse group. The *Schisandra*-treated show-jump horses completed the circuit in a shorter time than the controls

In an earlier study involving Thoroughbred horses a single dose of extract equivalent to 192 g of *Schisandra* fruit produced similar results to the above study. The race horses were on average 1.8 seconds faster over 800 m (Ahumada, 1989). It was postulated that *Schisandra* may cause a lower synthesis of lactate in muscles under anaerobic conditions and also stimulate lactate clearance by the liver. Significant reductions in serum levels of GPT, GOT, and creatine kinase was observed in poorly performing horses at days 7 and 14 after oral administration of standardized *Schisandra* extract ($P<0.01–0.05$) compared with baseline values. The sport horses selected for the trial had persistently high enzyme levels. Horses treated with placebo did not experience significant reductions in any enzyme.

Potential veterinary uses: To improve the detoxifying capacity of the liver, acute or chronic liver diseases, including hepatitis; chemical liver damage, poor liver function, preventing and treating oxidative stress in performance animals

Astragalus membranaceus

Astragalus has potent antioxidant activity. It increases red blood cell SOD and reduces lipid peroxide levels. The cardiotonic activity of astragalus may be related to its antioxidant activity. Of 14 Chinese herbs testes against lipid peroxidation in rat heart muscle, Astragalus was found to be one of the most potent.

Potential veterinary uses: Geriatric support, congestive heart failure, early heart failure, chronic infections, immune deficiency, cancer

Ginkgo biloba

Ginkgo biloba extract has significant antioxidant activity due to the flavonoid and terpinoid components. The antioxidant activity is most evident for cardiovascular events such as hemorrhage into tissues, ischemia and also retinal detachment. It also has anti-angiogenesis activity in solid tumors.

Potential veterinary uses: Cognitive dysfunction, cardiomyopathy where hypercoagulability is a concern, bronchitis and asthma, peripheral circulation disorders, central nervous system ischemia (ie, from trauma), hypercoagulation disorders, possibly stress (oxidative or induced by glucocorticoid excess) from chronic illness.

Zingiber officinale

Ginger contains high levels of antioxidants. A study investigated the effects of ginger root extract (GRE) on the viability and production of nitric oxide (NO) and prostaglandin E_2 (PGE_2) by sow osteoarthritic cartilage explants. GRE reduced NO and PGE_2 production by cartilage tissue explants suggesting an important role for GRE as an antiarthritic agent in osteoarthrosis in the sow.

Potential veterinary uses: Adjunct to cancer care and chemotherapy, osteoarthritis, improving circulation in geriatric or nonambulant animals

Table 1. Summary of Prevention of Disease with Antioxidant Herbs

Cancer and prevention of metastases	Turmeric, ginkgo, Green tea, Ginger, Grape seed
Cognitive dysfunction	Ginkgo, Schisandra, OPCs (Hawthorn, grape seed extract)
Cataracts	Ginkgo, bilberry, green tea, grape seed
Cardiovascular disease - including ischemia, retinal detachment	Hawthorn, astragalus, turmeric, dan shen, ginkgo, grape seed, bilberry, ginger
Liver damage	Silybum, Schisandra, green tea
Age-related processes	Green tea, ginkgo, bilberry, ginger, grape seed, any of the antioxidant herbs
Periodontal disease	Green tea

Table 2. Summary of Disease Management with Antioxidant Herbs

Cancer	Turmeric, ginkgo, Green tea, ginger, grape seed
Autoimmune disease	Turmeric
Inflammatory disorders	Turmeric, ginger, grape seed
Liver disease	Schisandra, Silybum, Dan shen
Pesticide poisoning	Schisandra, silybum
Cardiovascular disease	Hawthorn, astragalus, turmeric, dan shen, ginkgo, Grape seed, shisandra, ginger
Eye disease	Bilberry, grape seed
Diabetes	Ginkgo, bilberry
Peridontal disease	Green tea

References are available from the author upon request, and can be found in Wynn S, Fougere B. Veterinary Herbal Medicine. Elsevier, 2006.

IMPROVE TREATMENT OUTCOMES WITH VETERINARY ACUPUNCTURE

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Are you familiar with the Covey concept of “sharpening the saw”? It is a parable that addresses the need to periodically assess and update one’s working skills, instead of endlessly plugging along using the same, increasingly less applicable work tools. Whether you are a Covey fan or not, there is no denying that there are more diagnostic tools than the ones you already have – and use daily.

When you dig into your medical bag of tools, can you be confident that you have the right tool for the job at hand? Or are you relying on your comfortable, old, hand-me-down tools? Today we’re going to talk about two terrific tools that you definitely need to think about adding to your medical bag. Both are time-tested, efficient, and safe. Both take time to learn how to use properly, but they can change the way you practice. And, if you learn them, they’ll change the way you think about medicine and the way you approach your patients. In this article, we’ll talk about veterinary acupuncture and in companion articles in this proceedings, about traditional Chinese medical (TCM) diagnostics and herbal medicine, as well as their application to emergency care. TCM concepts pertinent to small animal urinary tract disease and skin disease are discussed in subsequent articles.

Acupuncture is the piercing or stimulation of specific points on the body, typically by means of a very thin, flexible needle. Stimulation of an acupuncture point causes a complex cascade of body responses and the release of various neurochemicals and hormones in the CSF and bloodstream. Acupuncture can be used to diagnose and treat specific patterns of dysfunction and can be used to maintain homeostasis.

LEARNING EFFECTIVE AND SAFE VETERINARY ACUPUNCTURE

There are many possible approaches to learning basic, effective veterinary acupuncture. All will involve approximately one year of your time, during which you can expect—with due diligence—to complete an extended acupuncture course and to master the basics of veterinary acupuncture. It is no more possible to learn good acupuncture skills during a weekend course than it would be to master the basics of small animal orthopedic surgery during the same time frame. You may choose to learn about acupuncture as a sole therapeutic entity, as is taught at one prominent and respected American veterinary acupuncture institute, or as a medical treatment that is just one component of a TCM approach, as is taught by two other extremely reputable institutions, including the original international course for veterinarians which is still considered the ‘gold standard” course. And, having learned acupuncture, you can choose to approach your patients from the traditional western medical approach we've all learned and are comfortable with, or from a TCM approach which may seem rather foreign at first. Once you've decided upon a philosophy and an approach, you will still have to decide whether to integrate acupuncture into your existing practice or to make to move to an entirely different sort of specialty practice.

Some of us may be happy, and satisfied, to learn about techniques that can be comfortably plugged into existing practice: far fewer C-sections or bloat cases, safe alternatives to nonsteroidal anti-inflammatory drug (NSAID) use, fewer cases where we have to admit to the client that there is nothing we can do. Others of us will be more intrigued than intimidated by a medical tradition that is independent of Western medicine, and we may elect to learn more about it. Regardless of our preferred approach, one thing is clear: acupuncture is a discipline that takes time to learn, more time to learn well, and more time still to practice it effectively and painlessly

In his chapter in Veterinary Acupuncture, author and prominent veterinary acupuncturist Dr. Sheldon Altman has this to say about getting started in veterinary acupuncture: "The most important quality in becoming a successful and legitimate veterinary acupuncturist is first of all to aspire to be as good a veterinarian as possible. It is the obligation of the veterinary acupuncturist to be familiar with current conventional techniques of diagnosis and treatment.......The second most important factor in becoming a legitimate acupuncturist is the veterinarian's knowledge of acupuncture....."

WESTERN AND EASTERN APPROACHES TO ACUPUNCTURE

Western (allopathic) veterinary medicine offers a reductionist, mechanistic, linear view of the world. Since Descartes' introduction of analytic, reductive reasoning in the seventeenth century, the focus of modern Western medicine has been to view the body as a machine made up of distinct and separate parts. The body became divided into systems, similar to the parts of an automobile. We still view the heart as a pump, the nervous system as a telephone network or a computer. According to Descartes, each part of the body can be further analyzed and its functions explained. To this day, we are focused on how things work; we all learn the details of innumerable cycles and cascades. In the mid nineteenth century, Louis Pasteur developed the germ theory of disease. While this theory permitted an examination of how epidemics occur (TCM had explored and completely developed this concept several centuries before) and how they can be effectively treated, it further fixed in many minds the concept of cause and effect with respect to disease. We still view symptoms as manifestations of disease, and it is considered a "cure" when we eliminate the symptoms.

We learn about diseases by learning about lists of symptoms. For a great many diseases, we learn standard treatment protocols. We apply these same protocols to many different types of patients, as long as their basic symptoms match the disease we want to treat. We sometimes view patients as a manifestation of their major symptom—"this bloat cow, that cardiac dog"—and we may ignore symptoms that don't fit the picture we are building. We take a problem-oriented history, examine the patient by body system, develop differential diagnoses, test our theories, and arrive at conclusions. We utilize an extended battery of tools, tests, and techniques to establish our diagnoses.

In the past few years, Western veterinary medicine has eagerly jumped upon the “”evidence-based medicine” bandwagon, which our MD counterparts began exploring over a decade ago. We are slowly discovering that many western medical practices, therapies, and treatments near and dear to our hearts hold up quite poorly when subjected to such scrutiny. TCM, by contrast, holds up to such scrutiny remarkably well. Acupuncture can certainly be learned and utilized using either an Eastern or a Western approach. It can be unsettling to learn that more than one approach—in fact wildly divergent approaches—can be used to explain the same phenomenon, and you'll need to decide which approach is for you. It is largely a matter of personal comfort with your existing view of how you and your patients fit into veterinary medicine and the world in general. We’ll review briefly how each system interprets veterinary acupuncture.

WESTERN VETERINARY ACUPUNCTURE THEORY

From a Western perspective, we could say that acupuncture and acupressure can be thought of as a way to influence the function of internal structures by external pressure or needling at pre-defined points. When we utilize acupuncture, we are piercing the acupuncture point in a very precise way, with a specialized needle. When we utilize acupressure, we are applying a broader-based, less precisely located, pressure over the point. Both techniques are time honored and work extremely well.

Externally, acupuncture points can be superficially identified as foci of increased electrical conductivity on the skin. Points can be easily located by instrumentation, and these localizable points correspond exactly to locations identified over 1500 years ago in China. Microscopically, acupuncture points can be identified by their characteristic structure. A published body of work documents their locations and morphology. Visible via electron microscopy, they are an exquisitely complex structure of vessels and nerves that occurs at no other place in the body. When we stimulate an acupuncture point, either by acupressure or acupuncture, we cause a complex cascade of body responses and the release of various neurochemicals and hormones in the cerebrospinal fluid (CSF) and bloodstream. Acupuncture can be used to diagnose and treat specific patterns of dysfunction and also to maintain homeostasis.

Needling or otherwise stimulating a point activates small diameter nerves which travel to the dorsal horn of the spinal cord. From there, they cross to the opposite side of the cord, enter the brainstem, and eventually innervate the hypothalamus and pituitary. These higher centers respond by releasing neurotransmitters including endorphins and serotonin which reduce the perception of pain. In addition, further inputs are dampened in a process known as descending inhibition.

Since acupuncture points are usually reflexively linked to distant sites such as internal organs and other musculoskeletal structures, tissue damage in those distant structures frequently is sensed as pain at the acupuncture point. In addition, the afferent impulse from the damaged structure constricts the venules of the point, leading to a build up of heat and edema. This focal accumulation of heat relative to the surrounding area can be easily perceived in part because of the thin epidermis overlying the point. Swelling is contributed to by the concentration of mast cells typically located at acupuncture points. This triad of symptoms— heat, pain, and swelling—often makes acupuncture points easier to identify. When we needle or apply pressure to the painful and swollen point, a second reflex arc is probably produced that eventually ends back at the inflamed structure after first entering the brain. Within the brain, three different centers are activated, resulting in the release of neurotransmitters that reduce the sensation of pain. In addition, blood flow through the damaged tissue is normalized, resulting in a reduction of edema and exudation and an improvement of microcirculation. The net effect is healing of the damaged tissue and an immediate relief of pain.

These network connections provide not only analgesia but an opportunity for the damaged tissue to heal itself, explaining why acupuncture is regularly curative in disorders that would ordinarily be viewed as requiring more definitive therapy. Numerous studies have demonstrated a favorable effect on hemodynamics and innervation to damaged internal tissues following stimulation of external acupuncture points.

In Western minds, acupuncture is largely viewed as a cause-and effect phenomenon. A great deal has been learned about the structure and physiology of acupuncture points and pathways, and the physiologic effects of acupuncture are well explained by western medicine. What is less understood is the mechanism of action. A number of theories exist; all partially explain why and how acupuncture works. None explains it fully. Current thought holds that these theories are interrelated. It is thought that the degree of involvement of each mechanism depends upon the acupuncture points used relative to the suspected disease process as well as to the acupuncture techniques used.

EASTERN (TCM) VETERINARY ACUPUNCTURE THEORY

Caveat: It is important to realize that most TCM practitioners would view the use of acupuncture alone as incomplete treatment for any given patient. Rather, they would utilize a balanced approach that might include dietary recommendations, exercise or massage, herbal therapy, and acupuncture.

TCM offers a coherent system of thought which is entirely independent of Western medicine. It is a logical and absolutely consistent medical approach that has been evolving for over two thousand years. TCM provides a holistic view of the world in which unbalanced energy patterns contribute to disease and disease contributes to unbalanced energy patterns; there is no cause and effect. Health and disease are viewed as interrelated, dynamic processes and, in an individual, as a microcosm of the world. What happens inside an individual is a reflection of what happens in the world at large.

When evaluating a patient, we recognize the importance of many things, which Western medicine is just beginning to consider relevant: social interactions, air quality, temperature and humidity, season of the year, nutrition, pulse, and tongue appearance. We place a huge emphasis on observing, and talking to, the patient, gathering a careful history, and fully evaluating the patient by using all of our senses. Symptoms are important guides to viewing imbalances, but we recognize that presenting symptoms by themselves don't identify disease. A given symptom may represent many different disease states, and several individuals exhibiting the same set of symptoms may in fact have wildly divergent disease processes going on.

There are no standard protocols, because we recognize that health and disease states are specific to the individual. Our goal is not to quickly eliminate symptoms, because when we eliminate symptoms all at once we lose our ability to understand how the body is responding to our treatment. Rather, our goal is to gently restore balance—symptoms will shift, on their own, in response to restored homeostasis.

Most veterinary acupuncturists find that in order to be more than minimally competent, they need to learn at least a little about TCM. Although the vocabulary and concepts at first glance sound strange to Western ears, they have withstood the test of time, and they do allow us to treat our patients as the individuals they are.

YIN-YANG THEORY

The underlying concept that supports all of TCM is the thought that a part (a symptom, a disease) can be understood only in its relationship to the whole (the patient). Symptoms are sentinels for disease but do not define a disease process. Nor are symptoms isolated entities; they are a part of a generalized body imbalance that can be identified, by careful questioning and examination. This concept of all things being seen as part of a continually cycling whole is called Yin-Yang theory. Yin (pronounced YEEN) and Yang (pronounced YAHNG) are simply labels that describe how anything functions in relation to itself and to the world. Yin is generally described as having attributes of cold, damp, passivity, and darkness. Yang is described as heat, dryness, movement, and brightness. Yin and Yang represent two opposing points of a continual cycle; they are not static. Yin becomes Yang; Yang becomes Yin.

THE FIVE FUNDAMENTAL SUBSTANCES

In TCM, there are five basic body components that are critical to physical and mental balance. These are Qi, Jin-Ye, Blood, Jing, and Shen. They are intimately interrelated and have many corollary organ relationships. The patterns of their imbalances—deficient or excess—and the affected related organs provide highly reliable keys to diagnosis and appropriate treatment. Acupuncture can be used to manipulate the quality of these substances in order to facilitate balance.

THE ORGANS

The TCM system of anatomy is based on functional relationships. Organs are defined by their functions and by their relationship with the Fundamental Substances, with other Organs, and with other parts of the body. There are few parallels between Eastern and Western organ systems. TCM recognizes six Yin and six Yang Organs. Briefly and simply, Yin Organs store, transform, and regulate the Fundamental Substances; Yang Organs actively break down, absorb, transfer, and excrete. Organs are paired in a Yin-Yang relationship. Each paired Organ system has a specific physiologic and psychological function.

- Paired Organs are (Yin Organ listed first):
- Heart/Small Intestine (HT/SI)
- Pericardium/Triple Heater (PC/TH)
- Spleen/Stomach (SP/ST)
- Lung/Large Intestine (LU/LI)
- Kidney/Bladder (KI/BL)
- Liver/Gallbladder (LIV/GB).

MERIDIANS

Meridians are the channels that carry Qi and Blood in a constant cycle throughout the body, allowing these substances to travel to Organ systems and allowing the Organ systems to communicate with each other. There are six main paired Meridians which correspond to the above-mentioned Organ pairs and many other Extra Meridians which may or may not be paired. Imbalance in an Organ can block or slow the spread of Qi through the related Meridian; likewise, damage to a Meridian can affect the related Organs. Acupuncture treatment of points along an affected Meridian can facilitate the movement of Qi to the Organ or Meridian to restore balance. Herbs can also affect specific Meridians and/or Organs, as can other TCM treatments such as exercise and diet.

ACUPUNCTURE TECHNIQUES

There are hundreds of acupuncture points on our animal patients. Precise knowledge of point location, depth, point suitability for the condition or imbalance being treated, and proper needling technique are mandatory before you begin treatment. Acupuncture is usually performed using one of the following techniques:

Acupressure, manual stimulation of specific acupuncture points, is an ancient technique used to stimulate the flow of Qi. It is an excellent technique to relax patients and to relieve pain. Most owners can be taught acupressure techniques for home use, to maintain or extend their pet's response time to traditional acupuncture.

Dry needle acupuncture is an ancient and extremely effective technique in which sterile, preferably disposable acupuncture needles are inserted into specific acupuncture points. Needle length and gauge varies with the patient, specific point, and needle technique. Developing an effective and painless needle technique requires considerable practice and should only be attempted by trained individuals.

Aquapuncture: Acupuncture points can be stimulated by injection of sterile solutions into the point, with a hypodermic needle and syringe. The solution continues to stimulate the point until it is absorbed. Aquapuncture enjoys most use in equine patients where it may be practical to complete treatment very quickly. However, hypodermic needles cause more pain and can cause tissue damage. Experienced veterinary acupuncturists often find that dry needle acupuncture provides superior results to aquapuncture. Still, a growing number of integrative practitioners are finding that good aquapuncture results can be obtained with use of substances such as injectable homotoxicologic remedies.

Electroacupuncture, the electrical stimulation of acupuncture points, is an effective technique for acute and chronic pain states, CVI patients, oncology patients experiencing chemotherapy-related GI side effects, and intervertebral disk disease cases. It is less commonly used for analgesia. Most electrostimulator units are convenient, cost portable and usually battery operated. Effective units allow the operator to vary the amplitude, mode, and frequency of the stimulation.

Moxibustion, or stimulation of an acupuncture point by heat, is an effective treatment for chronic pain, especially in the winter months. Typically, heat is applied at the tip of an inserted acupuncture needle; the heat travels along the needle shaft to the acupuncture point. Moxibustion is highly effective but caution must be taken to avoid burning the pet's skin. The typical odor of the herb used in moxibustion is highly recognizable to many clients and can cause some consternation in a crowded or poorly ventilated hospital. In-room switch-on ceiling ventilation directly to the out-of-doors is advised.

Gold bead implantation: In cases where prolonged treatment of a point is needed, sterile gold wire or beads can be implanted in the acupuncture point(s). Implantation is usually reserved for cases that cannot be treated traditionally (chronic severe seizure disorders; navicular disease). While results can be impressive with this technique, the risks of anesthesia, scar tissue formation, and migration of the beads must be considered.

IMPROVIED TREATMENT OUTCOMES WITH VETERINARY ACUPUNCTURE:

Pain

Hip dysplasia, spondylosis, degenerative joint disease (DJD), and disk disease patients make up the vast majority of my acupuncture patients. These are patients who, if responsive to acupuncture, will require regular treatment for the rest of their lives. Treatment is usually easy, results are predictable, and client satisfaction is exceptionally high. These are very rewarding patients to treat. Many clients become consistent sources of referrals.

Healing of Chronic Wounds

Chronic, non-healing wounds often respond favorably to the use of acupuncture in combination with topical herbal therapy. A substantial body of research documents the efficacy of electroacupuncture in stimulating healing of properly stabilized non-union fractures.

Oncology Patients

Everyone who has not been hiding under a rock for the past decade now knows the Ogilvie mantra: “Don’t let ‘em vomit, don’t let ‘em hurt.” Acupuncture benefits include relief of chemotherapy-induced side effects (GI; leukopenia), reduced pain, and improved immune function, sense of well-being, and remission time.

Immune-Mediated Disease

Acupuncture effects on humoral and cellular immunity have been documented in diseases such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), myasthenia, pemphigus, immune-mediated thyroid disease, and asthma.

Dermatologic Patients

Acupuncture releases endogenous corticosteroids (CS), suppresses mast cell degranulation, and increases circulating IgE. Dependence on corticosteroids, antihistamines, and antibiotics can be substantially reduced in most patients. See the article in this proceedings on TCM management of dermatologic disorders for details.

Seizure Patients

Seizuring patients often present with phenobarbital-induced hepatotoxicity and/or an inability to tolerate potassium bromide. Acupuncture can reduce hepatic enzyme levels and resolve GI intolerance of these drugs. It also can be used to reduce the dose of, or number of, medications in polypharmic seizure patients.

Neurologic Patients

Acupuncture is effective in early resolution of neurologic symptoms in CVA patients and is useful adjunctive therapy in the treatment of many myelopathies. Senile geriatric patients who have resumed infantile elimination patterns often respond well to acupuncture.

Renal Disease and Lower Urinary Tract Disease

Acupuncture treatment can improve quality of life for many geriatric patients with chronic renal failure (CRF) by increasing diuresis, limiting proteinuria, controlling nausea, anorexia, and anemia, and improving general attitude. Patients with cystitis, dysuria, and incontinence often respond well to acupuncture. Renal failure associated with cisplatin treatment has responded extremely well to acupuncture. See my notes on TCM management of urinary tract disorders for details.

Hepatic Disease

Patients suffering from hepatitis, fatty liver disease, and liver changes associated with drug administration (CS, phenobarbital, chemotherapeutics) often improve with acupuncture treatment. In addition to resolution of anorexia and related symptoms, hepatic enzyme values often improve dramatically.

Cardiovascular Disease

Acupuncture, when used in conjunction with appropriate herbal and medical therapy, often permits better management of patients with cardiac disease. Faster stabilization of congestive heart failure (CHF) patients is possible and many maintain well on very low doses of appropriate medications. Boxers with hypertrophic cardiomyopathy (HCM) and Dobermans with dilated cardiomyopathy (DCM) often stabilize longer that with traditional Western treatment alone. Specific acupuncture points such as GV26 are associated with profound sympathomimetic effects, making them particularly applicable to emergency use.

Respiratory Disease

Feline asthma, allergic bronchitis, and respiratory diseases secondary to cardiac disease have all been treated successfully with acupuncture. Emergency presentations of respiratory disease often respond particularly well to acupuncture, which can generally be performed at the same time and without hindrance to other life-saving measures. Specific points are discussed in the “”Crashbox” article in this proceedings.

Dystocia

I have performed only two C-sections since learning acupuncture in 1992.

Other applicable conditions (ones with which I have less personal experience) include reproductive disorders, behavioral disorders, and surgical analgesia.

PROFESSIONAL VETERINARY ACUPUNCTURE ORGANIZATIONS

American Academy of Veterinary Acupuncture (AAVA): The best group for gaining an introduction to veterinary acupuncture. Non-certified veterinarians interested in learning about acupuncture can join as associate members. The AAVA has an excellent newsletter, regional CE meetings, and holds an annual meeting, along with many meetings held in the US in conjunction with major allopathic veterinary conferences and the American Holistic Veterinary Medical Association. Membership benefits include membership in IVAS. You can contact the AAVA at: www.aava.org.

International Veterinary Acupuncture Society (IVAS): Chartered in 1974; the international group for veterinary acupuncturists. Irregularly published journal and newsletter, annual meeting with formal proceedings book, location varies around the globe. IVAS’s Web site is www.ivas.org.

CERTIFICATION IN VETERINARY ACUPUNCTURE

IVAS: IVAS provides the longest-established post-graduate education. Their course is offered each year in the US and another location. The course begins each year in fall and ends in the following spring. In addition to four half-week formal seminar sessions, extensive home study is required to successfully complete the exams. Certification follows attendance at all sessions, satisfactory performance on quizzes and practical exams given in sessions, successful completion of final written and practical examinations, many hours spent in preceptorships with other veterinarians certified in veterinary acupuncture, and acceptance of one peer-reviewed case report suitable for publication in the IVAS journal.

Other courses: (All offer approximately 120 hours of instruction):

- CSU: Focus is on Western approach to acupuncture utilizing a strong background in neurophysiology.
- Qi School: Balanced approach in which students may specialize in small or large animal acupuncture.

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NEW QUESTIONS, OLD ANSWERS: TRADITIONAL CHINESE VETERINARY MEDICAL DIAGNOSTICS

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Learning even a few basic diagnostic principles of Traditional Chinese Veterinary Medicine (TCVM) will allow you to view your patients as the individuals that they are, with signs unique to them, rather than as category-specific "cases." This, in turn, will allow you to develop treatment plans as individualized as your patients. Your success in treating your patients can expand as rapidly as you allow your diagnostic skills to improve!

The tenets of TCM, which we'll talk about in this article, are easy and intuitive to learn. Some may seem foreign at first glance – tongue and pulse, for instance. I was taught, in vet school, to use pulse-taking to discreetly determine whether euthanasia solution had achieved its intended effect. Tongue evaluation was largely restricted to determining whether a patient was cyanotic. Yet other basic TCM diagnostic techniques are common to those used by any good western practitioner: collecting a good history, conducting a thorough physical examination, and making time for questions the client might have. Even these techniques are much more fully developed in TCM, however.

GENERAL TCM DIAGNOSTICS

In TCM, disease isn't an enemy, and health and disease are not the opposing ends of a linear physiologic continuum. Disease, like aging, is a specific process of life. It results from the interaction of pathogenic factors and the body's vital energy, or Qi. A healthy body's self-regulating systems allow it to acclimate to an ever-changing environment, and a dynamic balance between Yin and Yang promotes very strong vital Qi. If the body has strong vital Qi, it can clear pathogens, restore balance in the event of an internal imbalance, and repair any damage the pathogen or imbalance may have caused. Ideally, it will do so in a dynamic fashion, so that balance is restored and normal body processes proceed harmoniously.

If a pathogen successfully affects the body in a persistent manner (either because the body cannot clear it or the body cannot repair itself, or both), symptoms and signs begin to be apparent. Symptoms are subjective abnormal sensations and thus, in our animal patients, are often more advanced when detected than they would be in us. Signs, or objective displays of symptoms, are more easily detected in our patients. When we observe a specific pattern of symptom that we have seen before and therefore recognize, we generally feel comfortable enough to call that a specific "disease". This allows us to embark upon further diagnostics to confirm our impression, and gives us the confidence to develop a treatment plan and to assess the results of our treatment.

In TCM, we rely largely upon pattern identification as a diagnostic strategy. A pattern refers to the collection of signs representing a given stage of a disease, and it provides the perspective for treatment. Yet we recognize that patterns can be fluid and that as such, our treatment approach must be readily modifiable. Some find it terribly frustrating that treatment in TCM can be so "slippery"; I find it endlessly intriguing and ultimately satisfying to know that there will always be a way to proceed, always a way to provide answers to a worried client, and always a way to bring comfort to my patients.

Western medicine is often viewed as a highly developed and extremely sophisticated medical system. The reality is that those of us trained in this medical system are, at best wonderfully sophisticated generalizers and "lumpers" who – despite an amazing variety of diagnostic tools - often fail when faced with patients whose presenting symptomatology deviate from the normal range of signs and symptoms that we have learned. Try as we might to follow appropriate diagnostics and therapeutics, a given subset of patients simply won't respond. What do we do? Most of us employ more diagnostics, more therapeutics, or we refer the patient for more of the same elsewhere. Interestingly, a similar subset of non-responders emerges each time – just under a different veterinarian's care! And our usual response? We either define a new disease process – often including the word "idiopathic" in the title; or we chronically medicate the patient; or we decide the problem has a psychological basis and we re-refer to another specialist who continues the treatment cycle.

What if we revised our mindset to consider that we have failed the patient rather than insisting that the patient failed the correct treatment? We could begin to consider the possibility that we failed to correctly diagnose the underlying problem by oversimplifying the issues related to that patient's disease.

Here's how to avoid failures in the diagnosis and management of any disease state: examine your patient thoroughly, and listen to what your patient is telling you. Your patient is never wrong. Utilizing traditional TCM examination and diagnostic techniques can greatly expand your ability to succeed instead of fail. I'm not suggesting that you abandon your western examination methods – rather, I suggest that you continue to utilize them while adding a few more simple and quick TCM exam techniques.

The four basic TCM diagnostic tools you need to know about are inspection; auscultation and olfaction; interrogation; and palpation and pulse examination.

Inspection includes evaluating your patient from the moment she enters the exam room. Quickly evaluate gait, bearing, vitality, overall appearance, vocalizations, and then conduct a full medical examination. Use your western tools every time – otoscopes and ophthalmoscopes are meant to be used! A thorough eye exam gives a good opportunity to evaluate the cornea, anterior chamber and iris (related to Liver/LIV); pupil and lens (related to Kidney/KI), conjunctiva and sclera (related to Lung/LU), canthal area (related to Heart/HT), and lids (related to Spleen/SP). Remember that Qi from all the organs rises to the eyes and that the Bladder/BL and Gall Bladder/GB channels originate at the eyes. Check the ears, the external opening of the Kidneys, for any excretions, which are very often diagnostic for internal disorders of excess heat (LIV, GB) or deficiency heat (LIV or KI Yin). Evaluate the nose, the external orifice of the LU and a point of penetration of the Stomach/ST channel, for discharges, dryness, or excess moistness; there are at least 8 distinct differentials for nose issues alone! Evaluate the coat carefully; the hair of the head is related to the health of KI and that of the body is related more to LIV. Qi, Jing, and Blood are also reflected in the coat. Examine the mouth, gums, and teeth, recalling that the mouth is the opening of the SP and that both ST and Large Intestine/LI channels go around the lips while the teeth and gums reflect the health of the KI and ST. Note the mobility of the neck; in addition to giving you a wonderful opportunity to evaluate your patient's chiropractic status if you have this skill, the tone of the neck muscles and vasculature will tell a great deal about the state of the LIV (stiffness, distended/pulsating vessels); the KI and SP (flaccidity); and will help you detect presence of any Qi stagnation or Blood stasis (pain, vascular distension with pulse knotting). Evaluate the thorax and abdomen for shape, symmetry, presence of any masses, and note the respiration – is the patient breathing from the chest or the abdomen? Evaluate the thoracic and lumbar spine, recalling that the GV and BL channels pass along this area while the Dai channel runs circumferentially (like a belt) across the lumbar area. Look for any cold or warm areas along the spine or any points of pain, turgor, or flaccidity, and evaluate their position. Often, these will reflect pathology in a specific organ relative to BL channel points. Or, they may represent an acute (warm) or chronic (cold) chiropractic subluxation. Inspect all the limbs, recalling that disorders related to the internal organs can sometimes be identified through changes in external acupuncture points along the channels on each limb. Note any areas of limb tenseness, spasm, rigidity, trembling, or flaccidity, as the limbs are often areas where evidence of external pathogen influence will be seen (hot/swollen/painful/reduced ROM joints). Carefully evaluate the skin, which reflects LU health and *wei qi* (protective Qi) status. Look for color changes (reflecting heat, Yin or Yang-type jaundice, or KI deficiency); swellings or growths, and note the location of any abnormalities seen. Lastly, evaluate the tongue. While a good, thorough description of what is evaluated in the tongue could go on for weeks and while tongue evaluation and use in TCM diagnostics takes years to master, there are a few very easy and quick to learn points you'll take home today. We'll approach evaluating the tongue as we do the neurologic exam: from general to specific.

- Is the tongue overall normal or abnormal looking?
- Is it appropriate for the patient's size and breed?
- Is there anything about the tongue that looks especially weird? Where and what?
- Is the color a nice, healthy pink, or is it another color?
- Is the tongue a normal shape or is it shaped oddly (thin, thick, short, long, asymmetric?)
- Is there any kind of a coating on the tongue? If so, what color and where is it?
- Is there any marking, growth, or crack on the tongue? If so, where?

Now, what does it mean? All of the organs, the Jing, the Qi, and the Blood physiologically nourish the tongue in some way, and thus the tongue will reflect pathology in any of these areas. We'll illustrate this with a PowerPoint "tongue review and quiz".

Next comes auscultation and olfaction of your patient. Listening to vocalizations, to the heart and lungs, and paying careful attention to odors is important because all are related to the patient's physiologic status and potential pathologic changes. It is possible - through inspection, auscultation, and olfaction - to detect organ and general body pathology far before laboratory changes will ever be noted. Even emotional pathology can be detected this way – be sure to attend Dr. Boudreaux's lecture on this topic for more information. In addition to the usual cardiac and respiratory evaluations we are all accustomed to, auscultation can tell us a great deal about the state of the Shen, about body excesses or deficiencies, and about specific Organ pathologies, most notably those of the HT, KI, and LU when we auscult the chest. Ausculting the abdomen can reveal pathology of the ST, SP, LI, SI, and LIV when we hear borborygmi, belching, and flatulence. Olfaction is another very detailed science in TCM. Fan of five element theory know about normal and abnormal odors associated with each element and, by extension, with each organ. Assessing specifics of the odors associated with flatulence, sweat, stools, urine, vomit, and any secretions from any orifice is a time-honored TCM technique that can reveal fascinating details about a patient's health.

Interrogation allows us to subjectively obtain details about a patient's main symptoms as well as any complicating symptoms. I try to always use the classic TCM "ten questions" as part of obtaining a full history. It is always interesting to check how many of these questions you might already be asking as part of a complete patient evaluation. I found, in fulfilling the most current American Animal Hospital Association requirements for medical record-keeping, that acceptable examination forms require that one document at least some version of all ten questions, just as Chinese physicians have been doing since at least the Ming Dynasty (1368-1644, approximate time of publication of the *Shi Wen* (Ten Questions/Ten Aspects to Interrogate in Verse). There are many versions of the ten questions; here is a simple one:

- Is the patient more hot or more cold? Where does the pet choose to rest? Sunshine-seeker?

- How much does the patient sweat? (Species dependent, you may be assessing skin/nose/footpads)
- Is there any pain? If so, where? When? How often? How long? Fixed or moving?
- Is there any vertigo, dizziness, or are there any other abnormal sensations?? Head tilt/staggers?
- What are the BM & urine like right now? What are they usually like? When did they change?
- How is the appetite? What does this pet eat? What else? What else? What else? Supplements?
- What are this pet's drinking habits? How much? How often? Actually drinking or just hanging out at the water bowl? What is the owner using as a measuring device for food and water?
- Energy status? Stamina? Is either one better or worse at certain times of day or night?
- Sleep habits? Where? When? How long? Dreams? Restless?
- Reproductive status? Cycling normally? Interested in breeding? Over/under-interested?

Obviously, there are other questions you will want to ask within the context of an office visit. However, these ten questions form the framework for making important decisions about diagnosis and treatment. As with tongue diagnosis, we can liken the "ten questions" to conducting a good neurologic exam – once you get the exam pattern down and repeat it conscientiously, it soon becomes second nature. Rather than formally sitting down and asking all ten at once, you can easily incorporate them into directed, focused conversation with the client as you are examining your patient.

Lastly, we'll consider pulse examination and palpation. In TCM, these are considered a single activity, but with two distinct methods. Pulse examination, like tongue diagnosis, is both an art and a science. Pulse-taking has been utilized in TCM since BC, times; it was formalized as a science with publication of the *Mai Jing* (Pulse Classic) during the Western Jin Dynasty (circa 300 AD). Its publication precedes the first monograph on tongue diagnosis, the *Ao Shi Shang Han Jin Jing Lu* (Ao's records of the Golden Mirror of Febrile Diseases), Yuan Dynasty, by nearly a thousand years. In our animal patients, we differ from the human patient custom of taking both radial artery pulses as well as pulses in an upper (head), middle (hand) and lower position (foot); we utilize just the femoral arteries instead. Some practitioners evaluate all three pulse positions at all three levels but most commonly, one position is used and is assessed at all three levels. Depending on the text utilized, one can draw various relationships between the pulse positions and the internal organs. Normally, pulses will vary with species, age, sex, utility of the patient, season, and other factors such as emotional status, food intake, and medications. However, pulses are highly patient-specific and thus changes over time in the same patient have great significance. While up to 37 different qualities can be assessed in the pulse, even the novice can quickly evaluate the following:

- Is the strength appropriate for the patient?
- Is the speed appropriate for the patient?
- Can the pulse be felt in all 3 depths (with light, medium, and heavy pressure over the artery?)
- Is the pulse regular/reflective of normal sinus arrhythmia?
- Is what you feel symmetrical?
- Do you feel anything weird when you feel the pulse?

Palpation, like pulse-taking is also an art and a science and fortunately, most veterinarians are quite skilled at palpation. In TCM, there are four aspects to palpation: light touch with the fingers or palm, "feeling" with slight pressure using the entire hand, pressing or firm pressure using the hand, and tapping or percussive activity to detect fluid accumulation or Qi stagnation. The entire body is palpated. Acupressure points are also palpated for heat, tenderness, stagnation, or accumulation. Diagnostic points such as association and alarm points are thought to be especially significant and reflective of specific organ dysfunction if they are found to be reactive or abnormal upon palpation. They can also be used as an indicator of treatment success, since they will normalize with appropriate treatment.

Once the full exam is completed, the TCM practitioner uses the collected data to develop an impression of pattern identification. Some patients "fit" a specific pattern exactly, just as we sometimes see in western medicine. Commonly, however, a patient (especially the chronically and multiply diseased, polypharmic, geriatric patients we so often see in veterinary medicine), are a mishmash of presenting signs. We may be able to get no further that establishing the answers to four basic questions:

- Is the location of the disease attacking the exterior (skin, muscles, hair, channels, vessel) or the interior (Organs, Qi, Blood, bone, Marrow) of the body?
- Is the disease a hot or a cold disease?
- Is the patient deficient or excess?
- Is the overall classification Yin (cold, interior, deficient) or Yang (hot, exterior, excess)?

If we can get this far, we are well along in establishing a diagnosis or at least how to proceed. But if we can't get this far, we can use other TCM diagnostic systems that will still allow us to proceed. For example, if we can identify a specific external or internal causative pathogenic factor, we can use pattern differentiation specific to these factors. If we can identify a specific TCM Organ as being affected, we can utilize organ-specific pattern differentiation. If we can only decide that the disease is a hot or a cold-type disease, we can utilize diagnostic systems specific to each type. If we can get no further than determining a general region of the body that is affected, we can use Jiao-specific differentiation, choosing treatment options specific to the upper Jiao (HT, LU), middle Jiao (ST, SP, LIV), or lower Jiao (LIV, KI, SI, LI).

It is worth noting that an astute Western-focused practitioner could elect to bypass any further TCM diagnostics once the full exam is completed, and successfully revert to a Western final diagnostic and therapeutic plan. Simply by virtue of having collected a far more detailed history and evaluation of the patient using the simple TCM tools discussed, any practitioner can effectively integrate this information into established treatment protocols and expect to achieve improved treatment outcomes.

As long as one takes a careful history; examines the patient thoroughly, completing all parts of a good TCM and western exam; asks any necessary questions to clarify the case; and then looks for a pattern that fits the majority of the significant clinical signs, it is really quite difficult for any practitioner to go wrong.

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SAVE THAT DYING PATIENT! THE TCM CRASHBOX

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There are abundant veterinary medical resources to suggest what should be in your crashbox, and most of them adequately prepare the practitioner for a successful resolution for the majority of medical emergencies. In this article, we'll discuss some simple additions that can improve your success rate dramatically—without requiring more space. In my small animal practice, the full contents of my crashbox fit into a five drawer rolling cart. The drawers are alphabetized without regard to whether the contents are allopathic or alternative: for example, acupuncture needles are nestled next to injectable aminophylline, and Yunnan Paiyao, an herbal medication for speedy control of even severe bleeding, shares space with venostomy sets.

ACUPUNCTURE NEEDLES

These belong in everyone's crash cart, for use in emergency treatment points. An advantage to the use of acupuncture in emergency medicine is that acupuncture needles can generally be placed while other supportive, more traditional emergency care is being provided without detriment to the patient. Emergency treatment points include points on virtually every body meridian. With rare exception, "point prescriptions," or combinations of points, are generally the most effective way to treat emergency patients, Locations for all points mentioned can be found in any good veterinary acupuncture text.

Use of acupuncture needles requires some degree of practice, because they do not have a cutting edge such as is present on a hypodermic needle. Effective sizes of needles for emergency use are usually narrow gauge and short. Two sizes, 0.22x13 mm and 0.20x25 mm, will generally be adequate. In the absence of acupuncture needles, I would not hesitate to use a 25-gauge hypodermic needle. However, the cutting edge of hypodermic needles represents an additional patient risk, especially if many are used. Acupuncture needles, by contrast, will rarely produce bleeding. Acupuncture needles are single use and require disposal in a suitable sharps container.

Suggested points and point combinations for a variety of common emergency presentations are listed below.

- **Abortion or parturition induction:** LI4; SP; SP6; CV2, 3,4,5; and KI11,12,13,14 stimulation for 5-10 minutes, using strong manual stimulation, will stimulate abortion or induction of parturition. I have not done a single cesarean section since I began using these points over 10 years ago.
- **Acute asthma:** LU9 and CV22 calm and regulate acute asthma. A special point not on any meridian, Ding Chuan, is also very useful, especially in feline asthma. It is located midway between the GV and inner BL meridian, at the level of the caudal end of C7. Especially in panicky felines, the superficial nature of these points makes laser use more effective than dry needling.
- **Acute vomition:** PC6 is exceptionally effective in relieving even extreme nausea and vomiting associated with hypovolemia, whether due to infection, chemo, motion sickness, or postoperative complications.
- **Acute diarrhea with hypovolemia:** ST36 combined with ST25 is very effective; in exceptionally weak patients, combine with CV8 and use moxa.
- **Cardiovascular collapse:** GV26 stimulation induces a profound sympathomimetic response sufficient to induce resumption of normal cardiac rhythm in a flat-lined patient. KI1and HT9 must generally be treated for several hours afterwards, at judicious intervals, to maintain a stabilized rate and rhythm.
- **Tachyarrhythmias:** PC5,6; BL15; ST9; BL1,2; ST1 all slow HR.
- **Ventricular arrhythmias:** PC6 increases the fibrillation threshold and in rabbits, is equally as effective as lidocaine. Sympathetic-induced arrhythmias are controlled well by simultaneous stimulation of PC6 and ST36
- **Dilated cardiomyopathy (DCM):** PC6 increases stroke volume and CO, increases LV outflow, and decreases pulmonary capillary wedge pressure. PC7 and HT7 improve systolic function in general.
- **Hypertrophic cardiomyopathy (HCM):** Traditional Chinese medical journals report the use of HT8 in improving LV outflow, stroke volume and CO. Use of PC6 worsened the same patients.
- **"Heartworm treatment crisis":** Needling of HT7; LI4; LIV8; LI11; and ST36 can help stabilize patients.
- **Equine colic:** ST2; BL21; BL25; ST36; CV1; Bai Hui.

ACUPRESSURE POINTS

Acupressure involves finger pressure over specific acupuncture points. Acupressure points can also be stimulated by use of needles; however, the following points respond especially well to digital pressure. The following points are so important and so useful, there is no excuse for any practitioner to not know them and not to teach them to their staff:

1. GV 26: Resuscitation point; profound sympathomimetic effect; Restores normal cardiac rhythm. This point is so well known that even cardiologists teach it in cardiac resuscitation lectures.
2. ST 36: Master point for abdomen; Direct innervation to upper GI; Indicated for vomiting, diarrhea, bloat, and colic.
3. BL 60: "Aspirin point"; potent pain relieving point anywhere in the body; contraindicated in pregnancy.

4. SP 6: Immune function; Master point for pelvic organs; Tonifies Qi, Blood, and Yin; Indicated for GI and genital disorders, allergy and immune disorders, fatigue and weakness.
5. LI 11: General heat-clearing (skin or bladder infections); cools Blood, clears Heat & Damp; stops itch; enhances immune function.
6. KI1: Very strong resuscitation point, generally used in combination with GV26. Helps "ground" the dying patient back to earth.
7. PC6: For relief of nausea to extreme vomition, especially in situations involving shock.

HERBAL MEDICINE

There are three herbal medications eminently suitable for use in emergency situations: Yunnan Paiyao, Ren Shen, and Zi Cao. Both Yunnan Paiyao and Ren Shen are available in formulations that are easy to administer (orally or rectally) even to a critical patient. Zi Cao is a topical ointment, which is very useful in the emergency management of extensive skin injuries, including burns and trauma.

Yunnan Paiyao is a patent herbal medication. The precise formula is a closely guarded secret of the Chinese government. It first came to Western attention during the Vietnamese War, when it was found in the possession of enemy soldiers who utilized it as part of their medical field kits. It is an exceptionally effective hemostatic when used either topically or orally. There is extensive scientific documentation to confirm its positive hemostatic effects. Decreased bleeding time and shortened in vitro and in vivo clotting times have been documented in rats, rabbits, cattle, and ponies. It may be administered before and/or during a hemorrhagic crisis and is commonly used for any of the following: internal and external bleeding tumors, sheared toenails, surgical bleeds, epistaxis, coagulation disorders (i.e. thrombocytopenia), gastrointestinal hemorrhage, abdominal trauma, aural hematomas, avian bumblefoot, OHEs in estrus, and oral/dental procedures. Doses for Yunnan Paiyao are as follows:

- Dogs: <15 kg = 1 capsule PO BID; 15–30 kg = 2 capsules PO BID; >30 kg = 2 capsules PO TID.
- Cat: 1/2 capsule PO BID
- Horse: 1 bottle or 16 capsules PO TID
- Bird: 1 capsule dissolved in water PO SID.

Ren Shen, or Chinese Ginseng, is a potent tonifier of the TCM Spleen and Lung and of Yuan Qi, the original source of all of the Qi (energy) of the body. It revives "collapsed Yuan Qi," a TCM diagnosis characterized by shallow respirations, shortness of breath, cold extremities, rapid weak heartbeat, and a feeble or nonpalpable pulse—a condition akin to what we would call hypovolemic end-stage shock. Extensive medical studies have documented Ren Shen's positive ionotropic effect on the hearts of dogs, cats, and rabbits. It is mildly vasoconstrictive and slightly increases BP. For shocky patients, tiny and frequent doses (0.5–1 g, hourly) are suggested. Known Ren Shen herb–drug interactions include MAO inhibitors, insulin, glipizide, glyburide, and tolbutamide. Of particular interest to some readers may be Ren Shen's documented amelioration of the impairment effects of ethanol on learning and memory processes.

Zi Cao Ointment is a proprietary formulation developed by a collaboration between an OMD and a DVM. It is exceptionally effective in treating trauma injuries, extensive degloving injuries, skin lesions, burns, and non-healing or poorly healing wounds. Zi Cao possesses antibiotic and antifungal properties. From a TCM perspective, it drains damp and heat, and moves Blood. Because it speeds granulation so effectively, it should NOT be used for puncture wounds.

HOMOTOXICOLOGY USE WITH ACUPUNCTURE

At least three homotoxicologic remedies have specific utility for emergency room situations: Traumeel, Hepar Compositum P, and Lymphomyosot. I typically inject these into appropriate acupuncture points or utilize a 'circle the dragon" aquapuncture technique.

Traumeel is the quintessential remedy for any injury characterized by tissue bruising, crushing, and edema. It is available in tablets, oral drops, oral vials, in a topical cream and a gel, in an ear drop (useful for ruptured eardrums) and in an injectable form. The common acupuncture technique of "circle the dragon" is very effective when used with injectable Traumeel. In this technique, tiny boluses of Traumeel are injected circumferentially to the lesion.

Hepeel, available in tablets and vials, is effective in bloat, colic, and anorexia cases, as well as in any case of severe unremitting diarrhea or nonspecific severe abdominal pain. It is available as an injectable and as an oral tablet.

Lymphomyosot is useful whenever there is extensive generalized tissue damage. Available as a tablet, oral drop, oral vial, injectable solution, and topical gel, it reduces edema markedly and speeds healing.

WEB SOURCES FOR REFERENCED CRASHCART ADDITIONS

- Homotoxicology products are available through Heel, Inc. at www.HeelUSA.com
- Herbal products are available through many sources; I utilize www.atimetohealherbs.com. Acupuncture needles are available from a number of sources. I utilize Hwa-To or Serin needles from Lhasa Oriental Medical Supply, at www.LhasaOMS.com.

EDUCATIONAL RESOURCES FOR THOSE NEW TO ACUPUNCTURE

AAVA: American Academy of Veterinary Acupuncture: The best group for those interested in learning about veterinary acupuncture. Non-acupuncture certified members are welcome to join as associate members. The AAVA has an excellent newsletter and a highly informative annual meeting that is rapidly growing in popularity and attendance. They also sponsor tracks at most major veterinary meetings across the United

States as well as at the AHVMA meeting. AAVA membership benefits include membership in IVAS, the International Veterinary Acupuncture Society. AAVA can be contacted at: www.aava.org

AHVMA: American Holistic Veterinary Medical Association. Founded in 1981, this American group includes veterinarians, RVTs, and veterinary staff interested in a wide range of holistic modalities, including acupuncture. They have an interesting quarterly journal and an absolutely superb annual meeting. This multi-tracked meeting includes presentations from a wide range of allied holistic groups, including the AAVA and groups affiliated with veterinary botanical medicine, homeopathy, and veterinary chiropractic. The AHVMA has recently added a specific technician track and an introductory day track to the annual meeting. This group is warmly welcoming to new members and to first time attendees. I make it a point to never miss this meeting! They can be contacted at: www.ahvma.org

TEXTS THAT SHOW AND DESCRIBE LOCATIONS OF AACUPUNCTURE POINTS ESPECIALLY WELL FOR BEGINNERS

1. Schwartz C. Four Paws, Five Directions: A Guide to Chinese Medicine for Cats and Dogs. Berkeley, CA: Celestial Arts Publishing, 1996.
2. Zidonas N, Soderberg M. Canine Acupressure: A Treatment Workbook. Parker, CO: Parker Printing, 1995.

TCM PERSPECTIVES ON URINARY TRACT DISEASES: PHYSIOLOGY, DIAGNOSIS, AND TREATMENT

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Are there extremely detailed, astonishingly precise, and very effective ways to evaluate and treat urinary issues besides the ones you already know about? Thankfully, there are – because we all face the frustration of doing exactly the right thing for refractory urinary tract cases with patients who stubbornly refuse to respond! One such approach is the diagnostic and therapeutic intervention opportunities found in Traditional Chinese Medicine (TCM). In 1992, I realized – while listening to a lecture on the diagnosis and treatment of urinary diseases in the International Veterinary Acupuncture Society (IVAS) course one afternoon– that what I was listening to represented a unique and better way to evaluate and treat the refractory urinary issues I faced in my patients every day. This immediately sparked a life-long interest in the principles of traditional Chinese medicine (TCM). Learning TCM allowed me to view the constellation of signs we call "cystitis" and "incontinence" and "renal failure" through another lens – one much more specific than the one I was used to using.

The tenets of TCM that allowed me to make this quantum leap in patient care are easy and intuitive to learn. They encourage us to view our patients as the complete individuals they are rather than as "cases." Viewing them as such will allow you (with the appropriate training) to develop treatment plans as individualized as your patients. Your success in treating these difficult patients will then expand exponentially. Are there additional holistic modalities you could choose to use, probably with good success? Yes! Once you open your eyes to the possibility of diagnostic and treatment options besides the ones you already know, you'll be amazed by the richness of what is available to you. In this article and the companion articles in this proceedings, we'll be emphasizing those within my areas of expertise and those in which I have seen remarkable success when all other treatment approaches have failed.

To a holistic or integrative practitioner, what is limiting about how we view cases from a Western perspective? In Western medicine, when we observe a specific pattern of symptoms that we have seen before and therefore recognize, we generally feel comfortable enough to call that a specific "disease." This allows us to embark upon further diagnostics to confirm our impression, and gives us the confidence to develop a treatment plan and to assess the results of our treatment. Western medicine is often viewed as a highly developed and extremely sophisticated medical system – and it does generally work well, until we are faced with patients whose presenting symptomatology deviate from the normal range of signs and symptoms that we have learned. When our treatment protocols fail, what do many of us do? We term the disease idiopathic or assign the failure to the patient, rather than place the failure where it belongs – with us, in most cases.

Despite this, Western medicine is still the predominant therapeutic mode used today, here in the United States. Given that this is the "gold standard" we are held to as veterinary practitioners, it goes without saying that an appropriate integrative medical workup always includes a thorough, all-systems Western medical examination, use of all appropriate Western diagnostics, and may include some elements of traditional allopathic Western medical therapy. Thus, in discussing urinary disease, we will assume that you have collected and documented a thorough history, that you have a good understanding of the exact nature and duration of the problem, appropriately obtained a sterile urine sample, thoroughly evaluated it, run a urine MIC and appropriate bloods, evaluated any crystals or calculi if obtainable, and radiographed, ultrasounded, and biopsied your patient as appropriate. Additionally, an appropriate Western medical follow-up protocol, on a schedule determined by the patient's condition, should always be established and documented in the medical records.

TCM DIAGNOSTICS REVIEW

In the previous articles, we covered the basic principles of a thorough TCM examination. As a brief review, we'll use them to consider, from a TCM viewpoint, how to evaluate and treat the conditions of "cystitis," "incontinence," and "renal failure."

Recall that in TCM, disease is not an enemy, and health and disease are not the opposing ends of a linear physiologic continuum. Disease, like aging, is a specific process of life, resulting from the interaction of pathogenic factors with the body's vital energy, or Qi. Healthy bodies have a better self-regulating mechanism, better adaptability to an ever-changing environment, and a very strong vital Qi. Thus, pathogen-clearing and internal damage repair proceeds harmoniously. Pathogens that affect the body in a persistent manner (either because the body cannot clear it or the body cannot repair itself or both) allow symptoms, or subjective abnormal sensations, and signs, or objective displays of symptoms, to become apparent.

In TCM, we rely largely upon pattern identification as a diagnostic strategy. A pattern refers to the collection of signs representing a given stage of a disease, and it provides the perspective for treatment. Patients vary over time and thus patterns can be fluid; this means that our treatment approach must be readily modifiable.

Utilizing traditional TCM examination and diagnostic techniques can greatly expand your ability to succeed instead of fail. Examine your patient thoroughly, and listen to what your patient is telling you. Your patient is never wrong. Do not abandon your Western examination methods – rather, continue to utilize them while adding a few simple and quick TCM exam techniques.

Recall that the four basic TCM diagnostic tools you need to know about are inspection, auscultation and olfaction, interrogation, and palpation and pulse examination. Details of each technique are included in my TCM Medical Diagnostics lecture.

Inspection includes evaluating your patient from the moment she enters the exam room. Quickly evaluate gait, bearing, vitality, overall appearance, vocalizations, then conduct a full medical examination. The ophthalmologic exam, specifically with respect to the urinary system, provides clues to the health of KI, BL, and GB. The ears, the external opening of the KI are often diagnostic for internal disorders of excess heat (Liver/LIV, GB) or deficiency heat (LIV or KI Yin). Recall that the coat is related to the health of KI and to LI. Examine the mouth, gums, and teeth, recalling that the teeth and gums reflect the health of the KI and ST. The mobility, tone, and vasculature of the neck will tell a great deal about the state of the LIV (stiffness, distended/pulsating vessels); the KI and SP (flaccidity); and will help you detect presence of any Qi stagnation or Blood stasis (pain, vascular distension with pulse knotting). Evaluate the thoracic and lumbar spine, recalling that the GV and BL channels pass along this area while the Dai channel runs circumferentially, like a belt, across the lumbar area. Look for any cold or warm areas along the spine or any points of pain, turgor, or flaccidity. Often, these will reflect pathology in a specific organ relative to BL channel points. Inspect all the limbs, recalling that disorders related to the internal organs can sometimes be identified through changes in external acupuncture points along the channels on each limb. Recall that from a TCM perspective, lower back and knee pain is often viewed as a KI issue. Carefully evaluate the skin; look for color changes which may reflect KI deficiency. Lastly, evaluate the tongue. All of the organs, the Jing, the Qi, and the Blood physiologically nourish the tongue in some way, and thus the tongue will reflect pathology in any of these areas.

TCM auscultation and olfaction of your patient - listening to vocalizations, to the heart and lungs, and paying careful attention to odors - is important because all are related to the patient's physiologic status and potential pathologic changes In addition to the usual cardiac and respiratory evaluations we are all accustomed to, auscultation can tell us a great deal about the state of the Shen, about body excesses or deficiencies, and about specific Organ pathologies, most notably those of the HT, KI, and LU. Olfaction is another very detailed science in TCM, as it once was in Western medicine. Even in Western medicine today, most of us can easily recognize – and know the significance of - the odor of uremic breath.

Interrogation allows us to subjectively obtain details about a patient's main symptoms as well as any complicating symptoms. Try to always use the classic TCM "ten questions" as part of obtaining a full history. Here is a simple version:

- Is the patient more hot or more cold? Where does the pet choose to rest? Sunshine-seeker?
- How much does the patient sweat? (Species dependent)
- Is there any pain? If so, where? When? How often? How long? Fixed or moving?
- Is there any vertigo, dizziness, or other abnormal sensations? Head tilt/staggers?
- What are the BM & urine like right now? What are they usually like? When did they change?
- How is the appetite? What does this pet eat? What else? What else? Supplements?
- What are this pet's drinking habits? How much? How often? Actually drinking or just hanging out at the water bowl? What is the owner using as a measuring device for food and water?
- Energy status? Stamina? Is either one better or worse at certain times of day or night?
- Sleep habits? Where? When? How long? Dreams? Restless?
- Reproductive status? Cycling normally? Interested in breeding? Over/under-interested?

As with tongue diagnosis, we can liken the "ten questions" to conducting a good neurologic exam – once you get the exam pattern down and repeat it conscientiously, it soon becomes second nature.

Lastly, complete your pulse examination and palpation. In TCM, these are considered a single activity, but with two distinct methods. Pulse examination, like tongue diagnosis, is both an art and a science. In our animal patients, we utilize the femoral artery pulse. Normally, pulses will vary with species, age, sex, and other factors such as emotional status, food intake, and medications. However, pulses are highly patient-specific and thus changes over time in the same patient have great significance. It is relatively easy to quickly evaluate the following:

- Is the strength appropriate for the patient?
- Is the speed appropriate for the patient?
- Can the pulse be felt in all 3 depths (with light, medium, and heavy pressure) over the artery?
- Is the pulse regular/reflective of normal sinus arrhythmia?
- Is what you feel symmetrical?
- Do you feel anything weird when you feel the pulse?

Palpation, like pulse taking is also an art and a science and fortunately, most veterinarians are quite skilled at palpation. In TCM, we palpate the entire body four times: first, with light touch with the fingers or palm, then with slight pressure using the entire hand, next with firm pressure using the hand, and finally by use of tapping or percussive activity to detect fluid accumulation or Qi stagnation.

Acupressure points are also palpated for heat, tenderness, stagnation, or accumulation. Diagnostic points such as association and alarm points are thought to be especially significant and reflective of specific organ dysfunction if they are found to be reactive or abnormal upon palpation. They can also be used as an indicator of treatment success, since they will normalize with appropriate treatment. Once the full exam is completed, the TCM practitioner uses the collected data to develop an impression of pattern identification. Occasionally, patients "fit" a specific pattern exactly, just as we sometimes see in Western medicine. Commonly, however, a patient (especially the chronically and multiply diseased, polypharmic, geriatric patients we so often see in veterinary medicine), is a mishmash of presenting signs. We may be able to get no further than establishing the answers to four basic questions:

- Is the location of the disease attacking the exterior (skin, muscles, hair, channels, vessel) or the interior (Organs, Qi, Blood, bone, Marrow) of the body?
- Is the disease a hot or a cold disease?
- Is the patient deficient or excess?
- Is the overall classification Yin (cold, interior, deficient) or Yang (hot, exterior, excess)?

If we can get this far, we are well along in establishing a diagnosis or at least how to proceed. As long as one takes a careful history; examines the patient thoroughly, completing all parts of a good TCM and Western exam; asks any necessary questions to clarify the case; and then looks for a pattern that fits the majority of the significant clinical signs, it is really quite difficult to go wrong.

TCM URINARY PHYSIOLOGY

We all recognize the organs of the urinary system in western medicine, and we conveniently divide them into upper and lower urinary tract organs and related disease processes. The western system is simple, easy to understand, and straightforward to utilize. But it just doesn't work for many of our patients. Try as we might to follow appropriate diagnostics and therapeutics, a given subset of patients simply don't respond.

What if we revised our mindset to consider that we have failed the patient rather than insisting that the patient failed the correct treatment? We could begin to consider the possibility that we failed to correctly diagnose the underlying problem by oversimplifying the issues related to urinary tract disease. And if we begin to look at urinary tract disease from a TCM perspective, we'd see that there is scarcely a body organ that *couldn't* be involved in diseases of this system, either directly or as a paired organ with another organ that is actively involved. Urinary tract disease is truly a "three-Jiao", full-body disease. Let's look at potential organ issues alone:

Suspect #1: Spleen. The SP role in fluid metabolism, and separation of fluids into "pure" fluids that go to the LU and "impure" fluids that go through further digestive processes in the SI and LI before being shunted in one form to the BL makes this TCM organ a possible culprit. If the SP is somehow impeded or disrupted in its role in fluid and food metabolism, normal movement of fluids will be impaired, causing Dampness or Phlegm accumulation. This can be associated with a variety of urinary health challenges, including pain, dribbling, incontinence issues, and even renal failure.

Suspect #2: Lung: It is said that the LU oversees the body's 'water passages," dispersing fluids to the skin and to the KI. When the lungs take in the Qi of the air, it must be "grasped" by the KI in order for both organs to function properly. If the LU is weak, descending LU Qi won't properly carry fluids down to the BL via the San Jiao/SJ. If the KI is weak, it can't control its orifices properly. Issues such as incontinence and poor urine concentration can result.

Suspect #3: San Jiao: The SJ is the body's highway system for fluids and other substances. When the SJ is disrupted in its role in water movement throughout the body, dampness will occur. Long-term dampness accumulation thickens dampness into Phlegm. Think of a compost pile – over time, it may heat up and even combust. Dampness and heat can be associated with pain, burning, abnormal urine patterns, and even urolithiasis formation.

Suspect #4: Intestines: The SI and LI, with "power" coming from KI Yang, separates the fluids coming to it from the ST, and decides what portion of the fluids goes to the colon and what goes to the BL. If impeded in this function, fluids will not move properly to the BL, and BL fluids can become turbid and thick, with eventual heat accumulation..

Suspect #5: Heart: Normally, the HT and KI enjoy a mutually beneficial relationship in which descending HT Yang warms the KI, allowing it to "steam" some of its Yin back up to the HT. This "steam" serves to cool and restrain the HT so it can act in a discerning manner to control the entire body in its relationship with the exterior world as well as with the interior of the body. If HT becomes overheated, its Yang does not descend, the KI become too cool, and incontinence and/or Shen disturbance can result. A hot HT can also cause vascular disruption, with hematuria as an end result.

Suspect #6: Bladder: The BL stores and excretes urine as we understand it to occur in western medicine, saving needed water for the body in the process. The BL also transforms some of the body fluids into Qi, which then helps to control the volume of fluid leaving the body. The BL carries out this transformative process with the help of other water and fluid-transforming Organs: SJ, LU, KI, and SI. When impeded in this function, the urine can become scanty, thick, and hot; or, polyuria with isosthenuria could result.

Suspect #7: Kidney: The KI role in urinary tract disease is far broader than how we understand it to be in western medicine. While adequate urine concentration in TCM is known to be a function of proper KI function, the role of the TCM KI is much more extensive. KI Yang provides the power to separate fluids in SI and LI, supports the Qi transformation of the BL, provides power to "steam" some of its Yin fluids back up to the HT to cool it and to the LU to moisten it, and powers the SP Yang functions of transformation and transportation. The KI also governs the lower orifices, ensuring continence. If the KI fails in any of these functions, a wide range of urinary disorders result.

"CYSTITIS"

Classic signs and symptoms of cystitis as we understand it in the western sense – stranguria, hematuria, bactiuria, pyuria, pollakiuria, urgency, and a thick bladder wall upon palpation - are readily apparent in most of our patients. If we broaden our understanding of cystitis to include the organ systems just discussed, a number of mental "clicks" happen. It becomes apparent that we very probably miss a wonderful opportunity to effectively diagnose and treat a wide range of health challenges before they manifest as a painful cystitis. Realization dawns that we definitely miss treating both overt cystitis and more subtle manifestations such as feline interstitial cystitis most effectively when we fail to address the underlying causative factors. A clear understanding that antibiotics are seldom the best answer develops. An understanding of the obvious link between chronic cystitis and diseases such as TCC emerges. And, we begin to realize that all those frustrating cases of overt cystitis symptoms with sterile urine have a recognized pathology which is easily treatable. Yet - if we smugly elect to treat cystitis manifestations with herbs instead of antibiotics without addressing the underlying causes, are we really doing more of a service to our patients than the veterinarian who prescribed amoxicillin without performing any diagnostics and called it a day?

What we currently understand as cystitis would, in TCM, be viewed simply as a downward movement of damp and heat to the lower Jiao and then to the BL, causing painful, frequent, and urgent urination with odorous yellow urine accompanied by a burning sensation. (Other causes of TCM cystitis exist, but we'll go with what you know). Several causes could be identified for this damp-heat movement. Regardless of cause, the damp-heat need not affect only the bladder. If it moved to other area organs instead, it could manifest as urgent, odorous, hot diarrhea accompanied by anal burning and possibly the passage of mucus or blood (LI); or as an odorous, thick, itchy vaginal discharge; or as a preputial discharge; or as a metritis or an orchitis. And in fact, similar seat-of-the-pants herbal therapies could be effectively employed for all of these conditions.

If we established a goal of addressing the underlying causes for the syndrome we call cystitis, we'd have to first look at acute onsets of damp-heat in the BL. Four or more forms, depending on source, can be identified.

1. *Heat Lin or Re Lin disorder:* Re Lin is associated with acute classic cystitis signs plus dribbling, a red tongue, a rapid pulse and, if not treated quickly by draining the damp and clearing the heat, can result in chronic inflammation. The urine is often very turbid and this form can be very painful. The appropriate classic formula is Ba Zheng Wan, and this is my preferred treatment, with possibly up to 10% Yan Hu Suo (Corydalin) added if pain is substantial, or up to 10% Fu Ling if dampness predominates. Other formulas that have been advocated are Ba-zheng Powder (Xie, hardly a change from the classic formula), or San Ren Tang and Si Miao San (Marsden). Appropriate acupuncture strategies to clear the heat and rain the damp are those advocated by Marsden (SP 9, LI 11, He-Sea points; BL 25, empirical; BL 27, BL She point) and Limehouse (BL 22,28; CV 3,12; SP 6,9). Any acupuncture text will list other points to consider.
2. **Stagnation Lin or Qi Lin disorder:** Qi Lin represents LIV Qi stagnation, which often occurs in association with stress (I see it in agility and show dogs as well as in many cats maintained in isolated or very cat-unfriendly environments), or in conjunction with LIV Blood deficiency (carb-loaded pets, for example). Wood type animal personalities are commonly affected. The stagnancy creates more symptoms of abdominal tenseness and irritability and less damp symptoms than seen in other forms of Lin disorders. The tongue is often lavender to purple, pulses are more wiry. Herbal strategies to calm the LIV, clear the heat, and move the Qi include Wu Yao Tang, Si Miao San*, or Long Dan Xie Gan Tang. (If there is a lot of LIV heat). Appropriate acupuncture points include those advocated by Limehouse (PC 6, ST 30, LIV 3,5,6,8, CV3,5) and Marsden (BL 18, LIV-Shu; BL 27, BL Shu; LIV 8, He-Sea point; SP 6, LJ Qi mover; ST 37, Sea of Blood).
3. Heart Fire: HT fire usually represents an Upper Jiao heat excess; multiple causalities exist. Regardless of the cause; when the HT is too hot, it affects not only the Shen, Blood, and nearby structures such as LU, but organs with which it has a close association, such as KI and its paired organ, SI. Marsden has made the observation that both HT and SI are organs of discernment; the HT discerns to engage appropriately with the external world, ruling how the body reacts to the external, and the SI discerns to engage appropriately with its internal world of separating turbid from clear. When either function fails, normal discernment fails. The organism as a whole becomes flighty, anxious, and easily agitated, and the SI fails to separate appropriately, resulting in less fluid being passed to BL. The HT-SI association also gives us another important diagnostic and prognostic clue that the HT needs treatment, not just the BL: affected animals, usually cats, often will resolve symptomatically and then, later, begin exhibiting inappropriate urination behavior. Untreated, they will also usually relapse with overt cystitis signs, with or without bactiuria. HT Fire is a frequent cause of owner give-ups and unnecessary euthanasia in feline patients. The urine is not only scanty; it heats up and actually feels hot when collected. The tongue is red with a redder tip (why?), the pulse is quite rapid, and other cystitis signs are as previously described; hematuria usually predominates. Herbal strategies to relieve both clinical signs and the HT Fire, include LDXGT, SMS, and Dao Chi San (Guide Out the Red Powder), which specifically conducts heat out of the HT channel via the SI. This formula is effective for both

excess and deficiency types of heat. Appropriate acupuncture points include classic points for cystitis as well as points to calm the Shen, including PC6, the HT and PC association points, GV 20 to descend the Yang, and ST 39, lower He-Sea of SI.

4. **Deficiency Fire:** Debilitated, geriatric patients often suffer from deficient Blood, Yin, or both. When Yin, the body's fluid nature, is deficient, Yang is relatively excess. This causes a relative heat condition, not truly excess in nature, but "hot" all the same. Just as one can get burned by holding a hand over both a low and a high gas flame on the stove, deficiency Fire can dry up the body's fluids, including the urine. The urine becomes thick, scanty, hot, and often cloudy. The condition is often not painful, and the BL may not be thick upon palpation; the body is reduced in its ability to respond. The tongue is red, dry, thin and possibly small, pulses are rapid and weak and/or thin; and the patient generally appears thin and weak, and possibly quite jittery or agitated. Many startle easily or are quite vocal but with a soft voice. Many present with concomitant CRF. Treatment choices must be focused on nourishing the Yin and gently clearing heat. Appropriate herbal formulas are Zhi Bai Di Huang Wan or Liu Wei Di Huang Wan. The former is a variation on the latter, with two herbs added to make it much more specific for clearing vigorous Fire. ZBDHW is my first choice, as few of these patients present in an early enough stage for the latter to be very useful. Marsden's acupuncture prescriptions for fulfilling the stated therapeutic goals include the KI Fire and source points (KI 2,3); BL 23, the KI association point; SP 6, intersecting point of the 3 leg Yin channels, and locally, CV 3.

An important reality check is the realization that many of these acute heat, damp-heat, and Fire patients are quite difficult to needle. Treating an angry, very painful, or very anxious and flighty patient via needling can be a real morning waker-upper. Instead, I will commonly go straight to herbs, or, since I practice integratively, will employ another pain-relieving strategy. Homotoxicology offers wonderful benefits to acute and chronic cystitis patients and, with the use of autosanguis preparations either orally or injected into just one or two acupuncture point with a 30-gauge needle, provides rapid relief of pain and inflammation. The role of chiropractic subluxations should not be ignored; inappropriate sympathetic or parasympathetic stimulation of the bladder or to an organ involved in proper water metabolism, secondary to a subluxation, is a frequently neglected cause of recurrent acute cystitis. Other therapies with documentable efficacy include ozone delivery to the lower Jiao via rectal or vaginal insufflation; QGM or other infrasonic therapy; joint support products such as Arthriease and Cosequin; injectable NSAIDs, such as meloxicam; and non-narcotic pain relievers, such as tramadol.

Chronic causes for cystitis-type syndromes generally represent inadequate treatment of an acute form of cystitis, such as Re Lin or Qi Lin. These can transform into Xue Lin disorder or secondary Blood stasis. Once Blood stasis develops movement of Qi, fluids and (obviously) Blood slows, nutrition to the BL becomes inadequate, toxins cannot be adequately removed, and entanglements of Qi, Blood, and Phlegm can develop. The bladder wall appears thick and engorged to necrotic-looking; in very severe forms of Xue Lin, tumors may develop. Severe interstitial cystitis is one form of Xue Lin; transitional cell carcinoma is another. The tongue is generally red with a yellow coat; the pulse is rapid; the bladder is extremely thick, painful, and friable; hematuria is prominent. In Xue Lin, an important treatment goal is to get the Blood moving; yet if entanglement is present, we must clear this first. Blood cannot move effectively against an obstruction, and forcing it to do so will worsen the patient and cause excruciating pain. This is one form of cystitis where I would turn to homotoxicology before going to herbal therapy, because I have found the matrix-clearing benefits of appropriate homotox remedies to be a better first-treatment step. Once the matrix – the framework through which the static build-up will have to pass – is clear, I will then turn to appropriate TCM herbal remedies. An appropriate herbal formula would be the lower Jiao-specific variant of Xue Fu Zhu Yu Tang (Drive out Stasis in the Mansion of Blood Decoction), which treats dysfunctions with the commonality of Blood stasis. This is Shao Fu Zhu Yu Tang (Drive Out Stasis in the Lower Abdomen Decoction), which is specific for Blood stasis disorders of the reproductive system, the lower back, and the lower abdomen, with or without palpable masses. I often add Yan Hu Suo for its Blood invigorating and stasis-removing (profound analgesic, anti-inflammatory, muscle relaxing, and pain-relieving) effects. For those who don't keep single herbs in stock, good effect can be achieved by adding a second formula that is Yan Hu Suo based Two very nice formulas are Evergreen's Corydalin formula and Dr. Zhao's Corydalis Compound. Evergreen's Herbal Analgesic capsules, a Dr. Richard Tan formula, also work very well for this and any other situation in which substantial pain is present.

There are also several different forms of cystitis-like syndromes recognized in TCM for which western medicine has no name. These are Shi Lin, Gao Lin, and Lao Lin.

1. **Shi Lin:** Sometimes called Stone Lin, this form is characterized by classic cystitis signs, plus crystalluria that can progress to stone formation with resultant urinary obstruction. The tongue is red with a yellow coat, which may be thick and sticky, and the pulse is rapid and wiry. Crystals and stones represent a more extreme form of dampness accumulation, with transformation into Phlegm and eventually into a more solid form. Appropriate treatment seeks to clear Heat, drain damp, and open the water passages so that the stones or crystals can be expelled. An excellent formula is Allen and Boudreaux's proprietary Stone Qi Formula. I have seen this formula resolve

crystalluria rapidly (MAP crystalluria responds much faster than calcium oxylate crystalluria; the makers claim to have seen MAP stones dissolve, but I have not seen this happen, preferring to take seriously affected patients to surgery before they obstruct). Acupuncture points suitable for BL damp-heat conditions would certainly be appropriate, plus BL 63 to remove obstructions from the BL channel, and BL 39 with KI 2, to remove obstructions from BL and free the water passages.

2. **Gao Lin:** Also called Turbid Lin or Cloudy Lin, cystitis of this type exhibits lots of thick, turbid urine, with mucus or clumps of pale to white debris in the urine. Microscopically, these clumps have appeared amorphous when I have looked at them. In the excess type of this pattern, the urine may grow organisms when cultured; in the deficiency form, it is usually sterile. Excess patients have a damp-heat type tongue and pulse and exhibit similar damp-heat signs. Deficient patients usually appear tired, thin, show a pale tongue with or without a coat and a weak pulse, and may have substantial lower back pain. Any good damp-heat formula we have discussed would be appropriate for excess patients. Deficient patients are often treated like Lao Lin patients (below) or with a specific and somewhat difficult to find formula, Gao Lin Tang (Cloudy-Painful Urine Decoction). Acupuncture protocols are similar to those for damp heat (excess form) and Lao Lin (deficiency form).
3. **Lao Lin:** Also called Fatigue Lin or Deficiency Lin, representing chronic disease with a KI Yang deficiency. When Yang is deficient, the patient is cold, weak, and shows more signs of dribbling than with other forms of cystitis syndromes. All signs are worse after exertion. The tongue is pale and sometimes flabby, and the pulse is weak. Treatment goals are to tonify the Qi and KI, raise the Yang, and warm the body. An excellent formula is Bu Zhong Yi Qi Tang (Tonify the Middle and Ascend the Qi Decoction), the classic Qi tonic formula for raising and strengthening the Yang. Acupuncture protocols might include the use of moxa over points such as GV 4 to strengthen KI's Fire of the Gate of Vitality.

"INCONTINENCE"

Incontinence is frustrating to treat because western medicine has such a poor understanding of the causative factors. It is truly a crapshoot with respect to deciding upon appropriate therapy, even according to the experts in the field. TCM recognizes many syndromes, and no two reference sources agree exactly how to differentiate incontinence from enuresis; some do not differentiate them at all. For reasons of time constraint, we'll discuss the top four that IVAS presents in their course clinical lectures, as they encompass many of the types others differentiate individually while introducing some that may be more specific to our animal patients: obstruction of the Dai Mai channel, KI deficiency, HT-KI disconnect syndrome, and urgency from damp heat accumulation syndromes.

1. **Dai Mai obstruction:** Picture this channel as a belt that is too tight, constricting what is under it, and obstructing the flow on either side of it. When stasis occurs in this or any other channel, flow of Qi and Blood is obstructed. Specific to the Dai Mai, KI Jing also "leaks", as does urine. This syndrome can also be associated with pain, weakness, or paresis of the lower back and hind limbs. Regulating the Dai Mai with appropriate acupuncture technique (GB 41, master point, SJ 5, coupling point, and GB 26-28, local points; after Marsden) facilitates a response that can be surprisingly quick. Marsden's suggested formula is Xiao Chai Hu Tang (Lesser Bupleurum Decoction), classically a formula that harmonizes "half interior, half exterior" or lesser Yang/Shaoyang disorders, to speed their resolution. I have had good success with Neuro Plus, an Evergreen specialty formula developed by Drs. Chen and Tan, plus electroacupuncture above and below Dai Mai.
2. **KI deficiency:** Deficiencies of any KI vital substance will cause dysfunction and inability to control the urine. We've already discussed syndromes associated with deficiencies of KI Yin; here we'll consider KI Yang deficiency. In addition to the signs discussed under Lao Lin syndrome, incontinence-specific KI Yang deficiency is associated with a need for frequent urination at night (why?) and feelings of exhaustion and dizziness (why dizziness?). Geriatric pets may present with symptoms of cognitive disorder more than dizziness, which is hard to assess in our patients. The treatment goals and protocols discussed under Lao Lin syndrome are appropriate here, too. If the deficiency is associated with a great deal of lumbar and hind limb pain, I will add either Qi Bao Mei Ran Dan* or Du Huo Ji Sheng Tang* – both will effectively improve comfort, warm the lower back and hind limbs, and improve Blood and Qi flow to deficient areas. Yan Hu Suo* is another consideration, for reasons previously discussed. Jin Gui Shen Qi Wan (Golden Cabinet Kidney Qi Pill) and Tu Si Zi Wan (Cuscuta Seed Pill) are effective. The former works well so long as there is not a tremendous discrepancy between KI Yin and Yang, since it both nourishes Yin and tonifies Yang. The latter is excellent for those patients who are severely deficient to the point of being alarmingly frail and constantly dripping urine (source Qi can no longer fill out the skin and flesh or distribute the Blood and Qi well).
3. **HT-KI disconnect:** This is an extremely interesting syndrome similar, in some ways, to the mutual relationship between HT and SI. Here, however, the relationship is between the HT and KI – the two rulers, if you will, of the most essential aspects of body physiology. When the KI and HT fail to support each other, the HT does not warm the KI and the KI does not send up its Yin to cool the HT. The HT Yang flares into HT Fire, and the KI becomes too damp, resulting in incontinence. Treatment protocols center upon acupuncture to facilitate descending the

HT Yang, and use of formulas that stabilize the KI. Jin Suo Gu Jing Wan (Lock the Essence Pill) works well in my hands. Others prefer Sang Piao Xiao San (Mantis Egg-Case Powder).

4. Urgency from damp-heat accumulation syndromes is another important cause of incontinence, and is easily treated using any of the damp-heat formulas already discussed for cystitis.

However, I am frequently referred cases of incontinence treatment failure that were treated absolutely appropriately from a TCM perspective. Why did these cases fail to respond? Many of them involved very obvious chiropractic subluxations, and the patient's incontinence resolved completely with appropriate chiropractic intervention. It is squirmingly uncomfortable to be the recipient of questions such as "why did my Doctors mess around for three years with first PPE and then imipramine and then DES and then herbs, when you fixed the problem by adjusting her back once?". Please, always remember to radiograph the lower lumbar area in any case of refractory incontinence, and if in doubt about the presence of a subluxation, consider a referral to a certified veterinary chiropractor.

If no subluxations are present, you are certain that there are no other mitigating factors, and the case appears to be chronic-damp heat, homotoxicologic intervention may be most useful. Consider oral or autosanguis preparations of (as is phase-appropriate) Gelsemium Homaccord*, Solidago compositum, Ubichinon compositum, and Plantago Homaccord, using appropriate points.

"RENAL FAILURE"

Renal failure is viewed as having both acute and chronic manifestations in western medicine, with vastly differing presenting signs, symptomatology, and prognoses. TCM views renal failure as a chronic condition, albeit a treatable condition. Many causes exist, but the main ones center upon SP deficiency, KI Yin deficiency, and KI Yang deficiency.

1. **SP deficiency:** This more reflects renal insufficiency than renal failure; most SP deficient patients with KI manifestations appear reasonably well. They are isosthenuric, but remain well hydrated, generally mildly polyuric and polydypsic, and their bloods show only mild elevations in BUN and creatinine. However, they are patients who are walking a thin line, because their KI essence is not able to properly support KI Yin and Yang – and without this, there is poor interaction between the two to "spark" the production of KI Qi. Treatment goals are to tonify the SP and ST so that these Organs remain strong and able to resist invasions of cold and damp that can affect the KI and related organs of water metabolism, and to promote normalization of SP transportation and transformation processes so that normal KI function is supported. Tongue, pulse, and appropriate treatment strategies have been discussed.
2. **KI Yin deficiency:** Untreated, mild KI Yin deficiency will eventually progress to HT Fire and gradual "top dry, bottom wet" disconnect. The upper portions of the body, under the influence of a too-dry and hot HT, "heat up", cause agitation, nocturnal restlessness, increased thirst, a dry coat, weight loss, and general feelings of heat and a desire to select cool surfaces on which to rest. At the same time, the KI Yang cools and sinks, causing polyuria and dampness-obstructive symptoms in the lower Jiao, lumbar area, and hind legs. The patient is weak, painful, and often constipated with a red dry tongue, a rapid pulse, and a feeble appearance that can be masked by agitated activity. Treatment goals are to tonify Yin, cool the HT, and descend HT Yang to warm the KI. Treatment protocols appropriate for deficiency Fire are appropriate here. If mental agitation is severe, calming formulas such as Tian Wan Bu Xian Dan (Emperor of Heaven Pill to Tonify Heart), or Evergreen's Calm ES are useful add-ons. I would not use Calm ES alone, however. While both formulas have strong Shen-calming effects, Calm ES, does not possess the slight Yin-tonifying qualities of TWBXD. If constipation is severe, use Run Chang Wan as adjunctive care.
3. **KI Yang deficiency:** If the KI Yang is weak, the same scenario as above occurs. This time, Yang deficiency signs predominate, with a more static tongue, a weak and deep pulse, and more dampness signs. The end result, of course, will be the same without treatment – Yin and Yang will increasingly separate, and the patient will die. Appropriate treatment goals and protocols are as discussed, with more effort to tonify the KI (BL 23, KI 3, GV 4). The best herbal protocol for patients with this stage of dysfunction is, fortunately, the pleasant tasting tonic formula, Ba Wei Di Huang Wan. Another good choice is Jin Gui Shen Qi Wan.

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TCM APPROACH TO DERMATOLOGIC DISORDERS

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If you are reading this article, perhaps you have a creeping realization there is something incomplete with your current approach to common skin conditions such as atopic dermatitis. How do you respond when you see patients with a seasonal allergy that responds to symptomatic treatment but reoccurs every year, usually worsens over time, and eventually starts occurring during non-seasonal times? Many times, owners of such pets insist that their pets are healthy – aside from their skin issues. Yet is not progressive failure to respond to appropriate therapy a suggestion of illness? Years ago, I decided that it was – and that I was just prolonging and worsening the underlying condition by limiting my treatment approach to relieving immediate symptoms.

Western approaches to the treatment of skin disorders excel in treating acute symptoms of skin disease. Antihistamines and steroids work well to relieve acute episodic symptoms, and they work fast. Very few integrative or holistic practitioners are able to relieve acute skin disorders as quickly. Yet allopathic approaches work less well when patients have seasonal disease or underlying causes for their disease. In these cases, success must be measured by more than immediate symptom relief – it must address the cause of the symptoms – and this is where integrative medicine shines!

Successful integrative treatment of skin disorders first requires retraining owners to realistic treatment expectations. Why is this case? Most of the cases that integrative practitioners see have been treated traditionally until response ceases, at which point the patient is generally transferred to a veterinary dermatologist's care. The dermatologist then treats the same patient until response ceases, at which point the patient may be transferred to an integrative or holistic practitioner. In my practice area – the Chicago metropolitan area – the second largest referral source to me is from a large regional dermatology specialty center. These are challenging patients to treat and response certainly does not come as quickly as when the patient received the first steroidal or antibiotic treatment from their primary care veterinarian. However, the owner's expectations may be that response will be as fast as when the patient first developed the skin disease. It is often difficult for clients to wait the 3 to 6 months that may be required to return the patient to a semi- balanced state of health. With a discussed understanding of the reality of the time frame needed to achieve a probable response in the face of long-term unsuccessful past treatments, owner's expectations generally become more realistic.

We all face the frustration of doing exactly the right thing for refractory derm cases with patients who stubbornly refuse to respond. Fortunately, there are a variety of established, medically documented, and very effective ways to evaluate and treat dermatologic issues besides the ones you already know about. In this article, we'll talk about a specific modality that you can use to improve your success with difficult cases: Traditional Chinese Herbal Medicine. Learning the basic principles we'll discuss today will allow you to view your difficult skin cases through a new set of lenses – ones much more specific than the one most of us learned, refined, and still use. Once you learn to view your patients as the individuals that they are, with signs unique to them, that will allow you (with the appropriate training) to develop treatment plans as individualized as your patients. Your success in treating these difficult patients will then expand exponentially.

TCM DIAGNOSTICS

Dermatologic disorders have been recognized as early as the Zhou dynasty (1100–221 BC), when it was noted that some skin disorders were seasonal in nature. They have been formally described as early as early as the 14th century, much earlier than Western medicine had an understanding of the pathologic causes of skin disorders. While dermatologic disorders were not evaluated by laboratory testing or skin scraping or by definition of the cause, successful treatment protocols were described for many types of skin disorders. Formal dermatology textbooks – in the western sense - were first written in the 1960s.

Traditional Chinese medicine (TCM) offers a distinct advantage over Western medicine in its treatment of many cases of skin disease, in that it focuses on treatment of the cause rather than merely relief of the clinical signs. As we've discussed, according to TCM one must look at the whole body in order to treat skin disease. One must complete a thorough examination and history before deciding on a treatment protocol. The ten questions, discussed in an earlier article, must be thoroughly reviewed. In completing the history, the season, location, and description of the lesions are most important. This information will help to determine the chronological order and depth of the disease process.

TCM, like many systems of alternative medicine, recognizes that the root of many cases of skin diseases is an inappropriate diet. As has been amply documented by numerous veterinary nutrition experts, many processed pet food diets are inappropriate relative to the known dietary requirements of carnivores. From a TCM perspective, the chief culprits in processed pet foods are high carbohydrate content, low moisture content and inappropriate ingredient selection relative to the energetic needs of the patient in question. Skin diseases caused by such inappropriate diets fall into two general TCM diagnostic categories we'll discuss: blood deficiency and dampness accumulation. Dogs tend to fall into the blood deficiency category and cats into the dampness category, although both imbalances are commonly found in both species. Most severe cases of skin diseases, if left untreated, progress to the more chronic TCM diagnosis of Blood Heat. This is the stage at which patients are commonly presented for euthanasia if their underlying disease state cannot be resolved. Given the TCM perspective of the importance of diet, it is scarcely surprising that diet is used as a therapeutic tool in the management of skin disease, along with appropriate herbal therapy and acupuncture where appropriate. A fourth common skin TCM presentation is not related to diet much at all – it is more a manifestation of a seasonal weather factor: wind. Wind represents invasion of an External Pathogen Factor (EPF) into the body, where it acts much like it does externally. We might characterize Wind as something that comes and goes, moves frequently, and varies in intensity. Skin lesions associated with Wind Invasion behave similarly.

TCM Diagnostic Differentiators

We'll discuss more specifically how to recognize and treat the conditions of Blood Deficiency, Damp Heat, Wind Invasion, and Blood Heat in detail, after reviewing some common skin presentations and how they "fit" into a TCM diagnostic framework. From a TCM perspective, we can differentiate skin disorders using the primary diagnostic modalities of tongue and pulse, as well as by characteristics of the symptoms, as follows:

Pulse Characteristics

Rapid and forceful: Heat or Damp Heat; Thin: Yin deficiency, and/or Blood deficiency; Weak: Blood deficiency and/or Qi deficiency; Wiry: Stagnation, pain.

Tongue Characteristics

Pale: Blood deficiency; Red: Heat; Swollen: Dampness; White coat: Dampness; Red with thick yellow coating: Damp Heat.

Itching

Red skin with rash: Heat; Extremely itchy with odor: Damp Heat; Itching with dry, small dander: Blood deficiency; Itching with moistness, ventral aspect: Dampness; Itching which moves around the body: Wind.

Location and type of Lesions

Inguinal: Liver; Nasal: Lung; Lips: Spleen, Stomach; Pustules: Damp Heat; Vesicles: Dampness; Nodules & cysts: Qi or Blood stagnation, phlegm, damp.

TCM CATEGORIZATION OF SKIN DISEASE

Blood Deficiency patients that are presented for evaluation often represent those patients with exceptionally dedicated owners. Why? Because Blood deficiency signs are often somewhat subtle, low grade, and very localized, with lesions that sometimes have substantially regressed by the time a worried owner has secured an appointment! Recall that deficiency implies a weakened response; so these patients show little heat, little itching, feel and look reasonably well. They often respond very well to the triad of antibiotics, corticosteroids, and fatty acid supplementation, but given their underlying deficiency status, their symptoms will recur time and time again if the deficiency is not addressed. In the absence of lesions, how might one recognize a Blood deficiency patient? Recall that Blood deficiency specifically implies poor peripheral circulation, in this case, to the skin. Hence, these patients will have dry, thin, "crepe paper" skin, a poor hair coat which often becomes most noticeable after a close grooming or shaving of a specific area of the body, a fine powdery dander, and a low grade itch. Think of geriatric Miniature Poodles as the "poster children" for dermal Blood deficiency manifestations! In addition to these dermal manifestations, patients may also exhibit KCS and musculoskeletal symptoms. Because Blood deficiency can affect the Shen, these patients may also show mild to marked degrees of obnoxious behavior: stealing or guarding food or toys, timidity, excessive barking, and "attack and flee" nipping behavior. Blood deficiency pulses will be thin and wiry, and the tongue will be pale, thin, and with little or no coating. Once appropriate herbal therapy and acupuncture have been initiated, and the patient has improved, long term consideration must be given to correction of the deficiency, by means of adjusting the diet, maintaining an adequate exercise program, and use of digestive support. The exemplar formulas for Blood deficiency is Si Wu Tang.

Wind Invasion patients typically present much more acutely with much more obvious signs that, once they develop, can persist for extended periods of time. Rashes and other eruptive lesions are typical, as is the involvement of other body systems. Wind Invasion patients, for example may present with both multiple hot spots that appeared "overnight," and acute vomiting, diarrhea, or neck and back pain. Wind lesions can vary, depending on what other EPF they are associated with. Wind-Damp lesions will be wet or greasy and possibly swollen or edematous; intact vesicles or papules are characteristic. Wind-Heat lesions will be more likely to be dry, crusty or with peeling epithelial collarettes, and the patient will be more pruritic when the skin is warm – these are the patients who often worsen after a professional grooming.

Tongue signs in Wind Invasion patients are highly variable, and more dependent upon the presence of other factors besides Wind, such as internal or external heat and/or dampness. In a pure early Wind Invasion, the pulse would be expected to be superficial; however, pulse is also heavily influenced by the presence of other EPFs or internal factors. Because Wind Invasion patients often have an underlying deficient condition which allowed the EPF to enter the body, they, too may require long-term attention to resolution of any underlying disorder. Look to Blood deficiency signs to often emerge after resolution of the Wind Invasion is achieved. . The exemplar formulas for Wind Invasion include Xiao Feng San and Si Wu Xiao Feng Yin.

Damp Heat patients are the ones that make everyone want to reach for their entire pharmacy at once! As their name implies, they are "hot and wet" in a most unpleasant way – these patients often have a strong, offensive odor noticeable as soon as they enter the clinic, thick caseous exudates from any affected body part, and oozing hot lesions. They smell and feel greasy even after a fresh bath, and are often obese. The "poster child" for Damp Heat? The American Cocker Spaniel with chronic otitis externa, lip fold pyoderma, pododermatitis, greasy seborrhea, axillary and inguinal moist pyoderma, and anal gland sacculitis. Another classic presentation is generalized demodecosis. Other Damp-Heat clues include frequent bouts of acute cystitis, flatulence, very odorous and noisy diarrhea, chronically elevated liver enzymes, conjunctivitis, and a unpredictably bad temper. The tongue is generally red to purple, wet, and swollen. Pulses are slippery to wiry, depending on whether the Heat or the Dampness predominates and the rate is normal to fast. Exemplar formulas for Damp heat include Long Dan Xie Gan Tang and Si Miao San.

Blood heat completes our quartet of common TCM dermatologic syndromes. Dr. Steve Marsden calls this syndrome the "point of convergence" of virtually all longstanding cases of skin disease. Heat of any kind, from any cause, can manifest as Blood Heat if it is present and untreated long enough. Untreated Blood deficiency, Damp Heat, and external Heat manifesting as an EPF can be root causes. Iatrogenic external Heat causes include deliberate insertion of a pathogen, as can occur with over-vaccination in an ill patient, or over-vigorous treatment of a deep pyoderma or abscess. The absolute characteristic of Blood Heat is intense and persistent itching, to the extent that affected patients frequently and severely traumatize themselves. The skin may appear hemorrhagic and may lack normal integrity. These patients often feel very hot; they are literally unable to cool themselves by normal circulatory processes because their Blood volume is reduced as the Blood heats and dries. As heat follows its natural inclination and rises to the Upper Jiao, the Heart and Shen often become quite disturbed, leading to agitation during the day and altered sleep patterns at night. The pulse is highly variable but usually rapid with elements of inappropriate flow: wiry, choppy, or knotted. The tongue varies from red to brown, depending upon the degree of heat present. The exemplar formula for Blood Heat is Qing Ying Tang.

TCM THERAPEUTICS – HERBAL OPTIONS

Antibiotic and corticosteroid therapies are no less useful to the integrative practitioner than they are to those who practice allopathically. From a TCM perspective, we can certainly exploit known TCM characteristics of such pharmaceuticals to benefit our patients. For example, corticosteroids are both very cooling and quite moistening. Thus, they will especially benefit those patients with hot, dry, skin conditions ranging from Wind Invasion all the way to Blood Heat. However, as overly dry patients improve and their skin rehydrates, corticosteroids can become too Damp producing over time and for Damp-Heat patients, they may actually worsen the skin condition with even short-term use. Severely Damp patients may become "cushingoid" much faster than would typically be expected.

Antibiotics, from a TCM perspective, tend to be both cooling and drying. Thus, they are often excellent short-term choices for Damp-Heat patients, but could seriously impact Wind or Blood deficiency patients, unless concomitant herbal or other supportive therapy is used to correct the underlying dryness. In patients with underlying Spleen deficiencies, characterized as we've discussed yesterday, antibiotic use can be associated with mild to severe GI symptoms unless appropriate Spleen support formulas are utilized.

Herbal therapy is exceptionally effective for acute dermatologic cases whenever traditional therapy is either inappropriate or has been rejected by the client. Such therapy is very often focused on the immediate health challenge and is often short-term, if no underlying excesses or deficiencies are present. Some practitioners elect to proceed in a somewhat allopathic fashion, utilizing a TCM herbal "equivalent" to an antibiotic or a corticosteroid. Certainly, such products exist, and range from single herbs such as Mu Dan Pi (one of the most potent CS-like herbs utilized in Chinese medicine) or Jing Jie (utilized for its very potent antihistamine-like effects) to complete herbal formulations for the treatment of specific skin disease, such as Evergreen's Silerex or Herbal ABX, or Kan's Dispel Dampness and Nourish the Skin formula.

For chronic dermatologic cases, herbal therapy is one of my preferred modalities, so long as an appropriate TCM diagnosis has been established, the client has a clear understanding of the time frame required for resolution of the health challenge, and the client is prepared to accept a frequent recheck schedule. It is important to remember that herbal therapy does not equate with freedom from side effects, and the practitioner must always be ready to address these promptly. As patients move from resolution of their immediate symptoms to resolution of their underlying excess or deficiency condition, herbal doses will require modification. I find that even the most carefully prepared custom formula is seldom suitable for more than a period of 4 to 6 weeks in this later phase of treatment, and early on, I expect to recheck my patients every 2 weeks at minimum.

Learning which herbal formula to use for all cases of skin disease, and knowing how to use it and modify it over time, is an exhaustive process. There is no foolproof short cut to learning this information. However, even beginners can have good success by adhering to a few deceptively simple principles: if the skin disease is wet, dry it; if hot, cool it; if dry, moisten it; and in mixed presentations such as Damp-Heat, assess which presentation predominates, and treat accordingly. For example, if you have decided that your patient meets many of the criteria for Blood deficiency; you can feel quite comfortable utilizing a basic Blood deficiency formula, assessing at a 2-week interval, and modifying accordingly. Below, in alphabetical order, are some commonly used formulas and their indications

Chu Shi Wei Ling Tang

AKA: Eliminate Dampness & Harmonize the Stomach with Five Herbs & Poria Combination Also from the Golden Mirror, this formula enjoys substantial use in human medicine for herpes zoster. It is actually a combination of a combination formula, incorporating older formulas used to dry and drain dampness from the middle and lower Jiao (Wu Ling Tan for urination issues plus Ping Wei San and Wei Ling Tang for stomach issues). In our animal patients, it is used to treat relatively mild Damp Heat and Blood deficiency symptoms. Because it does contain some warming herbs to dry Dampness it is NOT suitable for patients with a strong Heat component to their skin disease. It is safe (and indeed often required) for long term use, but should NOT be used in pregnant animals.

Typical tongue and pulse findings: T - sticky yellow coat, P –slippery.

Clinical signs and associated health challenges: chronic GI signs (vomiting, reduced appetite, soft stools) mild damp heat signs, increased thirst or appetite, moist pyoderma, soft stools, sensitive to diet changes, yeast otitis, allergic dermatitis, mild pyoderma.

Long Dan Xie Gan Tang

AKA: Gentian Drain the Liver Decoction. This one is in most herbalists' "top ten" must-have formulas for the treatment of Damp Heat conditions anywhere in the body. First formally mentioned in the Analytic Collection of Medical Formulas, dating from 1682, this highly versatile formula treats Heat and Damp Heat especially well when it is of LIV or GB origin. Why is this formula so exceptionally useful? Consider the topical distribution of the liver channel, its association with the San Jiao channel via the GB channel (both are lesser yang channels), and the LIV association with the eyes, mood, and all three Jiao when its function is disturbed. Because the formula is so strongly cooling, it is not intended for long-term use, especially in cases with SP deficiency.

Typical tongue and pulse findings: T- Red, sticky yellow coating; P - Wiry, rapid, slippery.

Clinical signs and associated health challenges: red, itchy eyes, KCS, corneal ulcers, uveitis, acute glaucoma, severe pruritis, aggression, moist hot pyoderma, moderate to severe itch, yeast infections, epilepsy, allergic dermatitis, hepatic encephalopathy, vaginitis, cystitis, pyelonephritis

Qing Ying Tang

AKA: Clear the Nutritive Decoction. This useful formula was first described in Systematic Differentiation of Warm Diseases in 1798, a period of history when epidemics of infectious diseases were sweeping China and killing literally hundreds of thousands of people. It was developed to treat advanced cases of heat at the nutritive (Ying) and blood (Xue) levels of disease – the deepest levels of disease. At this advanced level of heat-associated disease, the Blood literally becomes "scorched" and stasis can result. Other formulas that address this deep level of disease are not frequently used today, because they contain ingredients that are banned, such as rhinoceros horn.

Tongue and pulse are characteristic of extreme heat and dryness: T - Dark red, dry; P - Rapid, thin.

Clinical signs and associated health challenges: irritability, severe heat, erythema, purpura, thirst, restlessness, severe intense itch, heat intolerance, severe systemic bacterial infections, hemolytic anemia, demodectic mange, severe deep pyoderma. Consider this formula for immune-mediated diseases such as immune-mediated thrombocytopenia (ITP), immune-mediated hemolytic anemia (IHA), and myositis, as well as for leptospirosis, encephalitis, and any severe vaccine reaction

San Ren Tang

AKA: Three Seed Decoction. A contemporary to Qing Ying Tang, and described at the same time in the same text, San Ren Tang is more specific for acute systemic contagious disease characterized by Damp Heat – in other words, at a less severe stage of disease, when the pathogen is still lodged in the Wei and Qi levels of the body. Often, these pathogens will enter via the Lu and ST and initial signs are referable to these organs and may be flu-like in nature: cough, dyspnea, vomiting, and loss of appetite.

Tongue and pulse are thus characteristic of Dampness in combination with Heat: T - Thin white coating, possibly lavender & swollen; P – Wiry to rolling, thin.

Clinical signs and associated health challenges: itch, agitation, hematuria, heat intolerance, crystalluria, moist or productive cough, greasy coat, mild to moderate damp heat accumulation, constipation, IBD, chronic conjunctivitis, asthma gastritis, seborrhea oleosa, fungal otitis, allergic dermatitis, cystitis

Si Miao San

AKA: Four Marvels Powder. This formula will either fall on your "always used" or "hardly ever used" list – there seems to be no middle ground. It is a derivation of Two Marvels Powder, described in 1481 in Teachings of Zhou Dan-Xi. Later, Three Marvels Powder was developed, and much later in 1904, Si Miao San was described. While it scarcely rates a mention in herbal formularies such as Bensky and Barolet, it enjoys wide use by some of the most highly regarded herbalists in North America, who use it for virtually any Damp Heat condition. Tongue and pulse signs are characteristic of Damp Heat as previously discussed. Clinical signs & associated health challenges: Heat intolerance, odorous gas, odorous skin, rounded abdomen, oily coat, vomiting, increased thirst or appetite, low back pain, elevated pancreatic enzymes, chronic GI complaints, degenerative myelopathy, IBD, otitis externa, allergic dermatitis, Cushing's disease, pododermatitis, anal sacculitis, epilepsy, recurrent pancreatitis, suppurative vaginitis, cystitis, colitis. With protracted Heat, hind limb atrophy and weakness of the lower back and legs can be seen.

Si Wu Tang

AKA: Four Materials Decoction. Dating from the same time frame as Shen Ling Bai Zhu San, and published in the 1000s in the Imperial Grace Formulary of the Tai Ping Era, Si Wu Tang is the classically recognized formula for Blood deficiency. In humans and in animals, Blood deficiency can result from inadequate diet, acute or chronic blood loss, or imbalances in any organ related to blood production; in TCM, this includes the SP, LIV, and HT. Si Wu Tang is not indicated for treatment of acute severe blood loss; rather, it is most specific for LIV Blood deficiency. In our carnivore patients, this is a common sequela to the practice of feeding a kibbled diet. The formula is highly Yin-nourishing and Blood tonifying, and is very suitable for long-term use. However, if the Blood deficiency has resulted in the invasion of EPFs other formulas may be more suitable. Because it is so Yin-nourishing, it is not suitable for cases SP Qi deficiency signs that have resulted in Dampness. Si Wu Tang is exceptionally effective in the treatment of reproductive disorders due to Chong channel stasis secondary to LIV Blood Stasis.

Typical tongue & pulse findings: T – Pale to lavender, depending on the degree of stasis; P – Thin and wiry to choppy, depending on the presence and degree of stasis.

Clinical signs and associated health challenges: anxiety, frequent dreaming, noise sensitivity, mild liver enzymes elevation, mild joint pain, infertility, seborrhea sick, keratoconjunctivitis sicca (KCS), and poor hair coat with low-grade itching. Allergic dermatitis signs, if present, are typically mild.

Si Wu Xiao Feng Yin

AKA: Four Materials Eliminate Wind Decoction. Known since 1742 when Golden Mirror of the Medical Tradition was published, this formula is eminently suitable for Wind Invasion, especially when secondary to Blood deficiency. Based on Si Wu Tang with a number of herbal additions directed at expelling Wind from the body, it is most suitable for short-term use until the Wind Invasion is resolved. Once this is accomplished, treatment needs to be redirected to address the underlying Blood deficiency. Si Wu Xiao Feng Yin should not be used in cases of Wind Damp Heat Invasion, as it can worsen the dampness symptoms. Tongue and pulse signs are similar to those seen in Blood deficiency. (Tongue and pulses more typical of Damp-Heat Wind Invasion would be more rolling and forceful, and skin pathology would be expected to be more pronounced).

Clinical signs and health challenges: Recurrent superficial pyodermas and otitis, papular rash in abdominal and inguinal region, low grade itching, fine dander, red, rough skin, dry coat, poor hair growth, staphylococcal hypersensitivity, allergic dermatitis.

Xiao Feng San

AKA: Eliminate Wind Powder. In use since the 1000's and published in The Imperial Grace Formulary of the Tai Ping Era, Xiao Feng San is a nicely versatile formula suitable for either Wind-Heat or Wind-Damp Invasion. When these EPFs enter the body, they become trapped under the skin. Especially if there is an internal pre-existing Damp-Heat condition, the EPFs settle deeper and transform into what is called "Wind Toxin." Extreme itchiness with weeping red lesions over large areas of the body is pathognomic for Wind Toxin. This condition can significantly injure both Blood and Yin, which then aggravates the itchiness and lends chronicity to this health challenge. Patients with Wind Toxin often traumatize themselves and develop significant secondary infections. Xiao Feng Yin treats both the immediate severe itch and the underlying deficiency. Faster results are often seen when it is both taken orally and applied topically as a paste o active lesions. One of my favorite single herbs, Jing Jie, is a chief herb in the formula; it has potent antihistamine effects.

Typical tongue and pulse findings: T - Variable with redness, with a white to yellow coat; P – Rapid and superficial.

Clinical signs and associated health challenges: Severe allergic dermatitis urticaria, eczema, psoriasis, ringworm.

Xiao Yao San

AKA: Rambling Ease Powder. Dating from the same time frame as Xiao Feng San, this formula's name derives from its effect on LIV Qi. When the SP is deficient, the LIV becomes less efficient at properly directing the spread of Qi throughout the body – it is constrained, resulting in typical SP deficiency GI signs combined with Blood deficiency signs.

Typical tongue and pulse findings: T – Pale, lavender, possibly swollen; P – Thin and soft.

Clinical signs and associated health challenges: LV/SP disharmony, abdominal pain, vomiting, constipation, diarrhea, abdominal distension, loss of appetite, lethargy, irritability, anxiety, IBD, allergic dermatitis, chronic active hepatitis. In humans, this formula is used successfully for treatment of fibrocystic breast disease, PID, optic neuritis, and central retinitis.

Yi Guan Jian

AKA: One Linking Decoction. Published first in the Continuation of Famous Physician's Cases Organized by Categories in 1770, One Linking Decoction is named for its utility in treating Yin deficiency of the LIV and KI with concurrent Qi stagnation. When LIV Yin is deficient, LIV Blood is also affected; the resulting deficiency is associated with pain along the LIV channel, stasis and heat accumulation, and eventually, epigastric pain with reflux.

Tongue and pulse findings are typical of deficiency and heat. T - Red or pale, dry; P - Thin, wiry.

Clinical signs and associated health challenges: powdery dander, elevated pancreatic and liver enzymes, hair loss, itching, irritability, chronic vomiting, allergic dermatitis, KCS, hepatitis, fear aggression, recurrent pancreatitis, separation anxiety, chronic active hepatitis.

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TCM MANAGEMENT OF ATOPIC DERMATITIS

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In Stephen Covey's published data on time management for professionals, he references a four-part time management matrix (Figure 1). His matrix tool can be used to differentiate essential from nonessential actions that must be taken throughout the workday, and provides a framework for deciding upon the most time-efficient order in which to get them done. A version of his matrix appears below. His goal for most professionals? To "live north of the line" – in other words, to spend most of our working day proactively dealing with issues in Quadrants One and Two. By doing so, we can minimize the volume of interruptions from Quadrant Three and (hopefully) avoid being so overwhelmed that we take refuge in the time-wasters of Quadrant Four.

We can approach our treatment of atopy by use of a similar matrix. Many of the challenges we deal with in our atopic patients represent true "Urgent and Important" Quadrant One situations. They require immediate appointments and immediate diagnostics and therapeutics. Other patients—perhaps many—become Quadrant One patients because we failed to deal with their health challenges proactively in the past, to keep them from becoming emergency situations. (Many of our Blood Deficiency patients fall into this category.) Others represent patients we sometimes are tempted to deal with by benign neglect. Their owners frequently call at inconvenient times because, for example, their pet is keeping them up at night itching. These we often view them as Quadrant Three cases – Urgent, but Not Important. We prescribe a simple, immediate, and effective corticosteroid intervention to quell the itch. Then the patient re-presents a month later with a raging Damp Heat Quadrant One condition requiring immediate attention, extensive care, and a long period of follow-up.

Let's evaluate the dermatologic version of this matrix to re-prioritize how you could choose to treat your atopy patients. From a TCM perspective, are there Quadrant One patients? Certainly—and there are specific herbal remedies to address their needs. Therapy is likely to be short-term. When completed, we will need to address the underlying health issues that prompted the Quadrant One presenting status—otherwise, these patients will present repeatedly, acutely, and severely.

Quadrant Two is where TCM therapeutics definitely shine. This quadrant represents our opportunity for proactive, preventative, truly holistic care. Therapy is likely to be long-term, but can often eventually be replaced by careful and appropriate attention to diet and dietary supplementation.

Quadrant Three – Urgent and Not Important – represents another important opportunity for the astute TCM practitioner. By careful assessment of the underlying reasons behind minor nagging derm issues such as seasonal itching, we can often prevent these patients from becoming year-round medical nightmares.

What about Quadrant Four? From a TCM perspective, are there "Non-urgent and Not Important" medical issues associated with our atopy patients? I don't think so. Yet, until I learned TCM diagnostics and therapeutics, I had few good answers to give clients who complained that their pet sometimes smelled odd or had

Quadrant One **Urgent & Important** Crises, pressing problems, deadline-driven projects, meetings, and reports	**Quadrant Two** **Important, But Not Urgent** Preparation, prevention, planning for avoidance of crises and short deadlines
Quadrant Three **Urgent and Not Important** Needless interruptions, unnecessary calls, paperwork, e-mails, meetings; other people's minor issues	**Quadrant Four** **Not Urgent and Not Important** Trivia, busywork, irrelevant calls, paperwork, e-mails; time-wasters; 'escape" activities (TV, Internet)

Figure 1. Time management matrix.

a coat that wasn't shiny. Now, armed with a knowledge of tongue, pulse, and acupuncture point diagnostics, I truly believe I can say none of these patients have Quadrant Four problems. Quadrant Two is where these patients belong—along with appropriate herbal therapy and attention to diet and supplementation.

Quadrant One **Urgent & Important** Acute severe atopic flares QING YING TANG SI MIAO SAN LONG DAN XIE GAN TANG	**Quadrant Two** **Important, But Not Urgent** Proactive, preventative Tx SI WU TANG YI GUAN JIAN QI BAO MEI RAN DAN
Quadrant Three **Urgent and Not Important** "He's keeping me up at night with his itching" WEI LING TANG CHU SHI WEI LING TANG SAN REN TANG SI WU XIAO FENG YIN	**Quadrant Four** **Not Urgent and Not Important** "He's got a funny smell" "His coat isn't shiny" TCM: No such thing as a NU/NI !!!! Move to Quadrant Two

Figure 2. The Dermatologic Matrix Equivalent: Herbal Additions to Keep You "North of the Line"

OZONE THERAPY: BEYOND OXYGEN. THE MOST NEEDED ADJUNCT TO VETERINARY MEDICINE

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Ozone is one of the most beneficial substances on this planet, and the BAD science you hear quoted on the news every night is causing you to subconsciously be afraid of nature, and therefore, a part of life itself. They tell you that somehow hydrogen plus nitrogen or sulfur equals ozone. $H + N + S = 0_3$? Not on this planet it doesn't! What is ozone? Simply, oxygen. Three atoms of nature's oxygen. It exists in a very active form for about 30 minutes before breaking down into two atoms of regular oxygen by giving up one atom of singlet oxygen. Where does ozone come from? Nature. And nature is efficient. The new growth in the forests, the trees, the grass on your front lawn, and the plankton in the ocean are continually creating oxygen.

If you have seen *Inconvenient Truth,* the Al Gore documentary on global warming, there is one scene that brings it all together. In one section he discusses the CO_2 levels over the Pacific Ocean. In addition to the original measurements that began in 1965, they were able to measure the levels from hundreds of years ago by taking samples from deep within glaciers. Gore shows a graph and needs to get on a mechanical cherry picker to show you the levels in 2006. The levels 5 years from now go off the screen.

What this clearly shows is that we live in an anaerobic environment very different than 40 years ago. CANCER Thrives on CO_2. Thus, if we live in an environment that has high CO_2 we can expect more cancer. Dogs and cats age 6 times faster than we do and their entire life is living within this high CO_2 level. Should we be shocked that 46% of dogs and 39% of cats are getting cancer? They are the canaries in the coal mine and are showing us what cancer rates will be in humans. The World Health Organization (WHO) estimates that the rate of cancer in humans will be 50% by the year 2020. We need to bring more oxygen to the tissues so they can respond.

Interestingly, in the news recently, they talked about how soft drinks, either diet or sugar-based, increased heart attacks. If you are ingesting CO_2 every time you drink, it may be what causes inflammation. Whether it is your heart or any of your tissue, you are putting yourself in an anaerobic state. That should be contrary to homeopathy as well. Giving yourself an oxygen state must be positive and thus helps the vital energy move towards healing by giving it more oxygen.

As you read this, this oxygen is rising up into the atmosphere to where the ozone layer is. In the region of the ozone layer, our rising oxygen is bombarded by the sun's photochemical energy in the form of ultraviolet (UV) rays. The UV energy bombardment changes the oxygen from O_2, two atoms of stable oxygen, into O_3, three atoms of unstable active oxygen. We call this pure form of oxygen "ozone." The using up of the UV rays to create ozone is how the ozone layer shields us from their harmful effects. This is all part of the natural process of life on this living biosphere called earth. The chemical formula for this is $3\ O_2 > UV > 2\ O_3$.

Bringing in ozone therapy into a veterinary practice is one of the best and easiest ways to enhance therapies which we may already be practicing. Wherever we have inflammation there is an increase in CO_2 in the tissue and oxygen would benefit healing in that location. After doing over 4,000 ozone treatments at my clinic, the overwhelming success is seriously noticeable. Veterinary medicine can enhance the healing of the body and its tissues with ozone. It is affordable, easy to administer and potentiates our medicine. It brings down the inflammation and disinfects with oxygen and no harsh chemicals

WAYS OF ADMINISTRATION

1. Saline 0.9% percolated with Ozone
   - Subcutaneous fluid given to patients which gets into the blood stream and through the blood brain barrier
   - Flushing external wounds
     - Hot spots, bite wounds, post surgical areas,
   - Flushing gums and mouth before and after dentals with or without extractions
   - Flushing eyes and other orifices
     - Eye injuries and infections
   - Flushing and cleaning ears
   - Flushing infected surgical sites including abdomen
   - Flushing urinary catheterized animal to bath the bladder and cleanse surface
   - Bagging limbs and flushing areas that have infections or inflammation
     - Interdigital infection, toe infections, wounds, pyoderma, *Malasezzia*, tumors
2. Insufflated rectally
   - For whole body administration
   - To get into an inflamed colon
   - Direct uptake into the caudal mesenteric vessels into the liver
3. Ozonated air bubbled through water and virgin olive oil
   - Auricular bagging or through a stethoscope
   - All the above limb bagging for a lessened ozone odor and lung irritation
   - Whole body bagging
   - Whole animal placed in a close cage
4. Ozoned water
   - Drinking directly after making
5. Intravenous treatments
   - In horses, IV catheter placed in jugular vein; using small 25-gauge needle bubbled as a pure O_3 gas toward heart slowly
   - Also given with ozonated saline charged

6. Prolozone prolotherapy with ozone as a flush behind the B12, procaine, dextrose, and Homeopathic Combination. Use equal volumes of liquid to ozone.

PRECAUTIONS

1. DO NOT breath ozone directly, because it will cause irritation in lungs. If taken within lungs must go through olive oil.
2. Having the pets on vitamin C or other antioxidants is important to protect against free radicals.
3. Some bleeding can occur with thrombocytopenic patients at the site of the subcutaneous administration.
4. Warn clients that the subcutaneous administration is cold and pets may squirm as if someone has but a cold towel on their back. Good distraction with cookies or upbeat conversations will help.
5. Some dogs seem to have itching at the site so allowing them to "shake it off" after is good.
6. Keep windows open or have a vented area when bagging, as it might cause some to have irritation of the throat.
7. Always check the connections of the silicon tubing.
8. Use only silicone tubing, because it will break down regular rubber and some soft plastic or latex.
9. Be careful to keep any equipment that has black rubber away from the ozone. That includes anesthesia breathing bags as it will break down the rubber.
10. Ozone will dissolve latex gloves when as a gas.
11. Do not leave the ozonator on without the oxygen connected
12. Always use 100% oxygen running through the ozone generator; do not use room air.
13. Some people are sensitive to the ozone so make sure your techs or client are not having any sensitivities.
14. When placing rectal catheter make sure after removing you pull the tail between rear legs to prevent "passing of the gas" before it has a chance to be absorbed.

SUGGESTIONS AND APPLICATIONS

1. Before bagging the ears or wounds first flush well with the ozonated saline to clean off the surface; making the surfaces moist also helps the process.
2. Use the largest needle to get the fastest fluid administration and therefore have less O_3 converting to O_2 in the plastic tubing.
3. Keeping the IV line attached with a needle will allow a more directed flush onto the eyes and any direct area
4. When loading a syringe, the ozone is heavier than air so you need to keep the needle opening upward. Placing a needle with cap on it gives you more flexibility to where it is placed prior to administering.
5. When starting a cylinder with 1000 cc of ozone allow it to perk for 30 minutes at 1/8 oxygen and 10 setting
6. Ozone will stay stable for about 30 minutes, so use it as soon as you can to get the maximum amount stored in the saline.
7. Ozone stays longer in glass than the plastic.Giving the ozonated fluids cooled gives you more time to assure that the O_3 is still present.
8. If you need to warm the fluids, take a thin water bottle filled with warm water and at the end of the IV drip wrap the plastic tubing around the bottle.
9. When bagging or whole body try to seal the opening to keep leakage to a minimum.
10. Attachment of energetic discs like tachyon around the cylinder might even energize the water even more.

CONDITIONS TREATED

1. All types of wounds, skin infections hot spots, pyodermas, abscesses, rashes, allergic dermatitis, insect bites, gangrenous lesions, deep abrasions with road dirt contamination, severe contusions de-gloving wounds, postsurgical flushing directly on incision and area treated.
2. Chronic and acute Lyme disease
3. Giving ozone before giving any acupuncture or homeopathy to make the tissue more hydrated and oxygenated
4. Acute and chronic kidney and liver failure
5. Pancreatitis
6. Viral and bacterial diarrhea
7. Spinal and head injuries
8. Musculoskeletal injuries
9. Cancer adjunct therapy
10. Stomatitis and gingivitis
11. Ocular irritations, allergic and infectious
12. Yeast-filled ears and both acute and chronic otitis
13. Upper respiratory conditions both viral and bacterial
14. Autoimmune conditions
15. To use instead of antibiotics if there has been a reaction or toxic reaction.
16. Potentiates the acupuncture, homeopathy and chiropractic and other modalities as it brings more needed oxygen to the body.

RESOURCES

Ven-Mar Scientific Inc
P.O. Box 974
Hempstead, Texas 77445-0974
978-826-3863

LONGEVITY RESOURCES

www.ozonegenerator.com
1-877-543-3398

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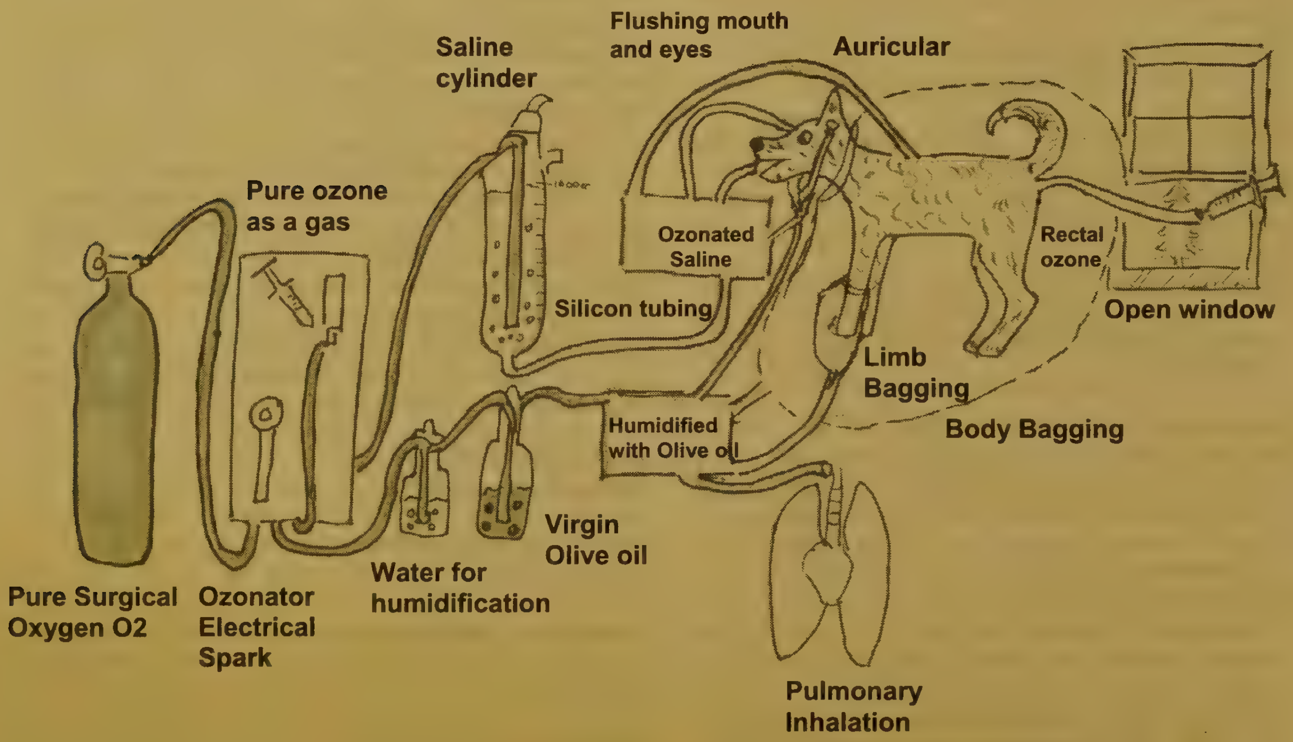
Table 1. Dosages and Settings for Ozone Therapy

IV fluids
Settings: Saline, 1/8 liter/minute and 10 setting

Animal's Weight (lbs)	Ozonated Saline (cc)	Restricted Amount (cc)	Rectal (cc)
10	70	40	25
20	100	60	45
40	140	100	60
60	200	140	100
80	250	180	130
100	300	200	140

Follow the recommended chart with your particular ozonator.
Ozone has the positive support for tissue repair and could be part of veterinary procedures.

Figure 1. Ozone therapy potentiates veterinary medicine healing with more O_2. After placed within body temperature it returns to 3 O_2 molecules



FOOD INTOLERANCE IN OUR VETERINARY PATIENTS

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Chomp, chomp, chomp...*Gulp*. Slurp, slurp, slurp...*Belch*. This is the sound of "Fido" eating his scientifically formulated, well-balanced dog food. It can be purchased at the grocery store, but the discerning owner travels to the local pet shop to buy the better quality food. Most people know that you get what you pay for in a pet food and that the higher grade foods come from certain recognizable manufacturers and can only be found at specialty pet supply outlets. But, is that axiom really true? Does purchasing the most expensive food guarantee that your pet will be receiving the best in nutrition that the industry has to offer?

The unfortunate truth is that pet food is not as scientifically formulated, as most would like to think. For the most part, Fido's food is made with convenience and cost of manufacturing in mind more than science. Yes, the first few ingredients look appetizing enough and there are essential nutrients such as vitamins and minerals added to the mix. But are these ingredients natural for the pet and are they readily available for absorption and use by their body? Herein lies the crux of the matter.

The wake-up call comes when one realizes that once the meat source is removed from the diet, the remaining ingredients are mostly unnatural for the pet. If we exclude the beef, poultry, fish, and lamb, the remaining calorie sources are mostly wheat, barley, corn, rice, and oats, all of which are man-raised crops that the dog and cat would never consume in the wild. I love to inquire of my clients "How would a pet get rice? Swim to Viet Nam?"

But what is the problem with these complex carbohydrates being in the diet? Humans consume these with every meal and they are doing just fine, aren't they? Ahhhh. Are we??? If we were thriving on these things, those reading this article would be doing something else right now, wouldn't they? The problem is that the grains listed above cause some universal problems among humans and pets alike, as do a number of other problem foods and food additives that eclipse even the grains in their contribution to health issues.

To digress for just a moment, I have been a veterinarian for 28 years. However, seven years ago I had something come along that changed my entire life—professionally, physically, emotionally, and even spiritually. I finally found, for the better part of my life, that I have been suffering from celiac disease, otherwise known as gluten intolerance or gluten sensitivity. For forty-something years, I suffered like most other celiacs from a myriad of symptoms, including allergies, heart burn and intestinal problems, depression/chronic fatigue, insomnia, memory and balance difficulties, joint pain, and even fibromyalgia. I was taking at least four prescription drugs daily, was caffeine addicted, and was quite frankly not having any fun anymore.

Within four days of eliminating all wheat from my diet, the recovery began...and it was *dramatic*. On day four, I felt like I did not need coffee for the first time in twenty years. By the end of the first week, my long-term heartburn was gone and my IBS symptoms were coming to a screeching halt. By the end of the month, my fibromyalgia, back pain, insomnia, and chronic fatigue were well on their way to being nothing more than a bad dream. I was shocked and amazed at the results of simply eliminating this “staple” of my diet and this incredible recovery led me into seven years of intensive, broad-based medical research.

During this phenomenal time, I created a Website (www.Dogtorj.net) to chronicle my discoveries. From there, I began doing Internet interviews and consultations, which led to more discoveries while I was attempting to help both pets...and their owners...with their chronic medical problems. My life had become *very* different.

I am now almost seven years gluten, casein, and soy-free, off all drugs (prescription and OTC), symptom-free, and feeling better than I did when I was twelve. Yes, this miraculous recovery got my full attention as a patient and as a doctor. How could this be? How could I have been suffering from what millions of people and pets are still experiencing, and yet, be completely well in such a short period of time? How could all of these conditions be linked together? That’s what I am here to share with you.

What I hope to convey to you in these three articles is the incredibly far-reaching effects of celiac disease and the related food intolerances and how they have been playing a vital role in the demise of our health and that of our pets. We will start by discussing the “big 4”...gluten, casein, soy, and corn, or what I now lovingly term “the four horsemen of the apocalypse”...and the roles they play in chronic illness, epilepsy and other “idiopathic” conditions. We will take a little stroll down memory lane—one of those 20:20 hindsight things—that will hopefully turn your head around and amaze you as much as it has me. You will see what we did to veterinary and human nutrition that has changed the course of our medical histories.

In addition, I hope to convince those of you who do not already know that the elimination of the “big 4” can result in absolute medical miracles, with rapid and lasting recoveries ranging from simple allergies and intestinal disorders to refractory epilepsy, multiple sclerosis, and peripheral neuropathies. Proper nutrition, of course, has a major impact on not only the quality of life we enjoy but also the life expectancy of both humans and animals. I hope to demonstrate that the overall diet of both pets and people coupled with the far-reaching effects of the food intolerances represent the most important factors that we have under our immediate control that will affect our overall health.

I am sure that most of you are now aware of celiac disease. Most of us were taught about gluten intolerance in the Irish setter, although from the response I have received from colleagues and even those who taught me medicine in school, this has been long since forgotten. However, seven years ago when my brother, father, son, and I all discovered that we suffered from this condition, gluten intolerance was considered a "rare disorder, affecting less than 1:5,000 Americans." In my very first week of research, I found that celiac disease was being diagnosed in nearly 1:100 people in the United Kingdom, Italy, and Scandinavia. This, of course, was totally incongruous with what was being reported in our (human) medical literature in the US, especially once our common ancestry was taken into account. I also found that 40% of first degree relatives to a celiac would have the condition, a figure that certainly applies to my immediate family (and one that makes us take a second look at those ancestors). Needless to say, that obvious dichotomy also fanned the flames of my developing passion for this newfound research project.

My personal diagnosis of celiac disease came about in an indirect fashion through my brother's medical woes. He had been experiencing weight loss and severe abdominal pain for a few months and had made two or three trips to the emergency room for sharp, unrelenting discomfort. After a complete workup, including extensive blood work, MRIs, barium series, colonoscopy, and more, his doctors were at an impasse. The only abnormal finding was an iron deficiency anemia. Little did they know that they held the key to the diagnosis in their hands.

Out of the blue came an e-mail from a friend of his writing to Bob about celiac disease. This close friend was a medical researcher and Internet buff who came across this "disease" as a match for Bob's symptoms. My brother brought it in to me—his "doctor" brother—to read one day in my veterinary hospital. When I read the pages from www.celiac.com, my mouth fell open and I said "Well, Bob. This is you all right. Trust me. When this many things fit, it is the answer. But, Bob! This is not just you, this is *me*! It describes all of my symptoms perfectly." And it *did*. My chronic fatigue, irritable bowel, insomnia, heartburn, allergy symptoms, and even my fibromyalgia were described on those pages. I immediately committed to going off all foods with gluten as well as launching a full-scale investigation into this elusive condition.

In the first day of researching celiac disease, I experienced the beginning of what I would later call "the revelation." As I read about the diseases states from which the gluten intolerant suffered, the celiac was rapidly becoming the "who's who" of illnesses in humans...*and* animals. We were absolutely gobbled up with allergies, IBD, immune-mediated diseases, and cancer, while suffering from staggering rates of hypo- and hyperthyroidism (Grave's disease), diabetes, lupus, rheumatoid arthritis, intestinal lymphoma, colon cancer, and much more.

Armed with the newest information that the potential number of people with celiac disease was 1:30 people, and that a myriad of medical conditions had been linked to gluten intolerance, and that wheat alone made up a whopping 30% of the calories in the standard American diet (and was the primary ingredient in our pet's dry foods), I started to have medicine make sense to me for the first time in 20 years...and "the revelation" occurred.

"But how *could* something as simple as wheat and an item that was as much of a staple in our diets cause such huge medical problems?" I wondered. It did not take long to find "the answer" (which would become the title of my first major paper).

In celiac disease, *gluten is* the culprit. Gluten is comprised of two components, glutelins and prolamines, the latter being the most troublesome protein portion. Glutelins are simple proteins found in cereal grains that yield amino acids when hydrolyzed. Prolamines are the storage proteins of the grains and are insoluble in water but soluble in alcohol and dilute acids. Gliadin is the real problem among the prolamines and it is gliadin that is found in most of the immune complexes of the major diseases we will cover. It is antibodies to gliadin that are the principal diagnostic aid in celiac disease. At 69%, gliadin makes up the majority of the prolamine portion of wheat.

The immune response to gluten is often insidious yet potentially devastating. Gluten is an innately sticky glycoprotein (which is used to make industrial adhesives) and does adhere to cells lining the intestinal tract, particularly those of the small bowel. Villous atrophy of the duodenum and jejunum results from a complex of immune responses directed at gliadin in sensitized individuals. The resultant increase in gut permeability allows unnatural polypeptides to enter the blood stream in an abnormal fashion, entering the infant and adult alike in biological forms that were unintended. These various polypeptides have both direct and indirect effects that are harmful in a myriad of ways. We will discuss "lectins" in a moment, the term used to denote antibody-sized glycoproteins from various sources, particularly from the "big 4" foods (gluten grains, dairy, soy, and corn).

So, the basic pathophysiology of celiac disease is that the glue-like gluten adheres to the villi of the duodenum and jejunum and then induces villous atrophy in sensitized individuals. Once the villous atrophy takes place, a number of serious consequences follow with the most critical being a chronic, insidious malabsorption syndrome. (And *here* is where I get a little crazy.)

How many veterinarians and doctors remember being taught in medical school what the duodenum *absorbs* in the way of essential nutrients? Not many do, according to my numerous conversations with my colleagues and MD acquaintances. In fact, I have had board-certified doctors look me in the eye and tell me that the duodenum absorbs "nothing." Then, when I have pulled the stake out of heart, I diplomatically correct them by explaining that I, too, thought that at one time until I learned differently through my study of celiac disease.

The fact is, not only does it not absorb "nothing," it takes in the vast majority of our calcium, iron, iodine, B complex, vitamin C, and numerous trace minerals such as zinc, copper, magnesium, manganese, boron, lithium, and more. Once we see this crucial part of our medical puzzle, "the revelation" begins and other important parts begin to fall into place. Osteoporosis, iron deficiency anemia, thyroid disorders, immune incompetence, and enzyme deficiency all have much more palpable origins. And the reason why the celiac is the "who's who" of what goes wrong with a human (or any other simple-stomached animal that is afflicted) suddenly becomes quite clear. We are malabsorbing the nutrients that are essential to our well-being while being bombarded by proteins that our body's deem threatening. And that is why I often refer to the duodenum as "Pandora's box"—damage that area and we unleash the multitude of plagues that await us.

But here is the bad news: Gluten is not the only culprit. I also found *this* out the hard way. As I stated earlier, within days of eliminating all gluten (wheat, barley, rye) from my diet, I felt better than I had in years. Symptoms were disappearing rapidly and I was totally amazed, catapulting me into years of research and "consumer advocacy." Yes, I was hooked for life and accepted my new mission with reckless abandon.

The most pressing problem was figuring out what in the world I would eat. (Later I would write the paper "What in the World Do I Eat?") Surely I enjoyed the weight loss that quickly followed my new dietary commitment but some frustration set in as I scrambled to find "clean" (gluten-free) foods. I had always avoided cheese and eaten limited amounts of ice cream because of the battle of the bulge but, "Hey, I can eat all I want now because I'm losing weight and they are gluten-free." So, I started putting cheese on everything, drinking more milk, and eating a lot more ice cream as dessert. And, within weeks my symptoms were all coming back- the heartburn/IBS, headaches, joint pain, fibromyalgia, brain fog/depression, and insomnia. "What is up with this? Milk is supposed to be nature's perfect food." I quickly found out differently…and why.

Because I had found that wheat was the number two human, dog, and cat food allergen and that the culprit, gluten, was used to make industrial adhesives and that the allergies were formed at the time the damage was done to the gut, I naturally asked "Where is the 'glue' in milk?" That is when I found that gluten has an evil twin and its name is casein. I found that casein is the glycoprotein that makes up 80% of the protein content of cow's milk…and the one that Borden uses to make Elmer's Glue. "Ahhhh. Now we're onto something."

So, I eliminated all dairy products and, in a few short days, my symptoms were disappearing again. Within 3 weeks my chronic shoulder pain resolved, my sleeping improved, and I was feeling better than I had in my entire life. But the quest for what to eat had just gotten more complicated.

I began substituting soy products for the dairy-drinking soy milk, eating soy cheese, and having soy-based "ice cream" for dessert. However, within a couple of weeks, my stomach was in an absolute knot and many of my symptoms were returning, especially the pain and insomnia. "Now what is up with this?" I exclaimed. "I thought soy was supposed to be a health food." It took less than an hour on the Internet to be convinced that we had all been duped into thinking that soy was healthy for us. And yes, soy *is* used to make industrial adhesives as well. In fact, they make super-glues from soy, which are commonly used in the automobile industry (eg, to stick your rear-view mirror to the windshield).

When I eliminated the soy from my diet, my health returned and my research project expanded. As hard as it was to believe that the main three foods thought of by most to be among the healthiest things we can eat…wheat, dairy, and soy…were, in fact, the absolute worst possible things for many people to eat, this incongruity fit well with other things I was learning were upside down. These things included the aforementioned lack of knowledge concerning the duodenum's function, the true incidence of celiac disease, and the fact that we used fever-reducers to stop virus-induced fevers and carcinogens to treat cancer.

Therefore, I was not surprised to find that corn was the fourth guy on the list, rounding out the "four horsemen of the apocalypse," a term I love to use when being melodramatic or "prophetic." Once I had eliminated the first three "riders" I realized how crummy corn made me feel when I ate it. One more trip to the "glue" list and I found that they did indeed make glue from corn. The best they could do, however, was to put cardboard boxes together with it. "No wonder it was the most tolerable of the big 4." I thought. And, in fact, it is tolerated better by humans, dogs, and cats than are wheat, dairy, and soy. The history of the pet food industry sure proves this.

Now this part is really fascinating to me. The retrospective look at my veterinary career and the history of pet food ingredients dovetailed perfectly with my studies concerning food intolerance in people. When I graduated from veterinary school in 1979, the vast majority of pet foods were made with corn as the carbohydrate source. Pets were doing "OK" on these foods, with a rather select group of dog breeds having unusual difficulty with allergies, immune-mediated diseases, and early cancer-related deaths. Our allergy-suffering breeds were little white dogs like the Poodle and Westie. Other trouble breeds were Cockers, Beagles, Boxers, Golden retrievers, Irish setters, and German shepherds—those experiencing allergies, immune-mediated diseases, and higher rates of cancer. The average dog was reasonably healthy and allergies were just *a* problem within the dog world, not *the* problem. Immune-mediated diseases were something that we actually got excited about seeing as doctors and diagnosticians, not something that made us wonder what the world was coming to when we would later see them come in three at a time. Cancer was always a major cause of death of pets but, again, not something that we would, in the relatively near future, get so "ho-hum" about, seeing mast cell tumors every month and watching dogs drop like flies by age 6.5 years of bone cancer and lymphoma. Suddenly, we were talking about medicine during our lunch hours rather than our golf games or our significant other.

What happened? First of all, we had a "wheat glut" develop in this country. It was a definable geopolitical phenomenon that resulted in wheat becoming cheaper than corn. Suddenly, the pet food industry started to make food, particularly dried kibble, out of wheat instead of corn....and Pandora's box was opened. It was during this time that we adopted the "interesting" routine of mixing in a new food with the old for 3 to 4 days. Why did we do this? Well, if we didn't blend it gradually, the pet would often develop diarrhea or even vomit on the newly introduced food.

Now let me stop right here and ask an important question...or three? Where in the world were our brains at this time? Why did we not suspect that something might be wrong with the new food if it caused diarrhea, much less vomiting? Were we really *that* out of touch with medical reality? The thing that fooled us was the fact that the pet "adapted" to the food so quickly if we mixed it in. And, it seemed logical to mix in a new food, so "Problem solved!" right? But in retrospect, we were truly asleep at the wheel, not understanding the impact of the new wheat-based food and having long since forgotten our lectures on gluten intolerance in the Irish setter (if we ever got one). This went right over our heads, including that of yours truly. So, I am not throwing stones but "Man, were we stupid or what???"

But out of this quagmire arose what would become a giant among pet food companies—Hill's Science Diet. They claimed that their foods were scientifically formulated to produce less allergies, less skin problems, less intestinal upset, and even smaller stools. And they did! So, what did they do to accomplish this? Basically, all that they did was not take that big "left hand" turn that everyone else did choosing the wheat route and Hill's stayed on the corn road. How simple. How wise! Wow!!!

Yes, corn *was* better tolerated than was wheat. That did not make corn perfect by any means but comparatively speaking, it was heads and shoulders above this newest mistake that was being made—the single worst mistake made in veterinary nutrition—the transition to wheat-based diets. Thankfully, this came at the same time that we made one of the best decisions in pet nutrition—to take the dairy out of dog and cat foods. Many of you remember milk-coated puppy and kitten chows. Those my age will also be able to testify that they have seen a reduction in asthma, rheumatoid arthritis, and type 1 diabetes since the dairy was removed from these foods, especially when it is pointed out to them. In a medical study I found 4 years ago, it was boldly stated that our children who get cow milk in the first five days of life have a 40 to 50 times higher rate of these three conditions. Understanding lectins (which we will cover later) will pull this all together for you.

And in retrospect, the trouble breeds mentioned above do have more problems with corn to this day (and maybe more, thanks to the genetic modification of today's corn. Do you remember CRY9C or "Starlink" corn and the Taco Bell shell recall a few years ago?). I believe that it is highly likely that the "big 4" food intolerance share the genetic tendency that celiacs experience in that 40% of first-degree relatives will have the condition. Therefore, I recommend the elimination of corn from the diet of all pets (and people who will listen) but particularly from that of the breeds mentioned above. I have now developed a strong suspicion of corn intolerance in these breeds by doing food allergy tests and seeing a high rate of corn allergies among them.

Thankfully, there are those in the pet food industry who are wising up, with more and more of them proudly stating and displaying on their bags "no wheat, no corn, and no soy." Unfortunately, they know that wheat is a problem but they obviously don't understand *why* it is so harmful or *why* it is now the (new) number one food allergen in dogs and cats. They turn right around and use barley and rye—the other two gluten grains—as substitutes. They must not understand celiac disease and the fact that the allergies are formed at the time the gluten induces the villous damage. Is that really the extent of their nutritional research?

It must be quite limited as dairy products are making a major comeback. (Errrrh!!!) Yes, even some of the most dedicated and "holistic" pet food companies are utilizing cottage cheese, skim milk, and yogurt in their newest formulas. When I call or write to these companies, they try to ease my dissatisfaction by stating that it is all lactose-free. Once again, is that the extent of their research on the topic of dairy intolerance? Do they not know that lactose is just a little 'ol sugar and that the proteins in cow milk, particularly casein (and even more specifically alpha s-1 casein), are the true culprits? Unfortunately, many are under the misconception that lactose is the main issue in milk.

However, as celiac disease becomes better known (and the awareness of this all-too-common condition is rising rapidly), the truth about casein, soy, and corn intolerance will finally emerge. *Then*, we will have "the four horsemen" on the run and people will learn that they *do* have their health destinies, as well as those of their pets, more in their own hands than they have ever believed.

VIRUSES AND LECTINS – THE MISSING LINKS

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The role of viruses and lectins in the development of disease has been one of the most amazing topics that I have researched over the past seven years. I include these together because there is a fascinating interaction between these two entities that helps to explain many of the conditions we still refer to as "idiopathic," a term to which I now take exception. The only concept that upsets me more is "autoimmune disorder," a term that implies that our immune system does not know what it is doing. I wholeheartedly disagree with that premise and a better understanding of viruses and lectins supports my dissent.

Let's start with lectins. In my quest for solutions to "idiopathic" problems, the study of these antibody-sized proteins/glycoproteins yielded answers to many of the questions that were haunting me as I tried to explain how my dietary changes could yield such phenomenal results. Lectins are carbohydrate-binding glycoproteins or proteins that are ubiquitous in nature, with plants, animals, and even bacteria producing these remarkable compounds. Although the true role of lectins in plants is still under investigation, we know that these proteins play numerous important roles in animals and humans. They serve to bind circulating glycoproteins to cells, such as those in the liver, to facilitate their removal. Our body produces lectins that are involved in immune responses (eg, mannose-binding lectin), the adhesion of cells, and the removal of pathogens through binding to carbohydrates on their surfaces. In the case of neurons, the oligodendrocyte produces two different lectins—one that helps nourish the neuron and another that can kill it. Bacteria produce lectins that enable them to adhere to tissue. Finally, certain foods contain lectins that can do serious harm to susceptible individuals. Therefore, there are "good" and "bad" lectins in nature—those that promote health and others that contribute to disease.

For the purposes of this discussion, the focus will be on those dietary lectins that have been directly linked to illness in animals and humans. The most common sources of damaging lectins are the gluten grains (wheat, barley, rye), dairy products, legumes (eg, soy, peanuts, beans), and corn. The nightshade family (tomatoes, potatoes, peppers, eggplant and tobacco) also contain potentially harmful lectins, most of which are inactivated by cooking but to which some individuals can become quite sensitive (eg, arthritis). For example, uncooked wheat flour, beans, and eggplant are considered toxic while heating them removes most, but not all, of the harmful lectins. Fermentation, sprouting, and soaking have also been employed to remove these harmful substances. But I frequently tell people to think "peanut allergy" when considering the degree of sensitivity that some individuals develop to these proteins.

The literature describes the pathomechanism of the damage done by these lectins as being like a lock and key, in which the circulating lectin serves as a key that unlocks the cell to which it attaches. All complex cells, plant or animal, have carbohydrates that project from their cell membranes. These serve as glycoprotein receptors (docking stations, if you will) to which circulating lectins and other things can attach. When the right "key" comes along, its attachment can initiate a cascade of events in that cell wall that may lead to a number of different outcomes, ranging from the attraction of the immune system and cell death to the production of hormones and chemicals to the multiplication of that cell.

Once I found that these harmful lectins (especially those from gluten, dairy, soy and corn) could cause inflammation and tissue damage all by themselves, without an immune response, things really started to make sense. The immune response is actually *secondary* to that damage, which helps to explain why we see such a variation in the *measurable* response in different individuals challenged by these glycoproteins. Some will respond with an outpouring of antibodies yielding positive tests while others will not, thus helping to explain the negative tests in individuals who ultimately respond quite well to the elimination diet when they employ it despite those negative tests.

It then becomes clear that these dietary glycoproteins are also a big part of what we label as "autoimmune disease." Personally, as I stated at the outset, I do not like nor do I use that term anymore unless I put it in quotes. That term implies that the immune system is attacking its own host's tissues for no good reason. I contend that this does not happen...ever. The immune system *always* responds appropriately but we simply do not always fully understand why it does what it does. The inflammation being incited by lectins is a prime example of this.

As stated, lectins are antibody-sized entities. How would we know they are present when they are, in fact, that small? We can't see them in a routine tissue sample. It would take biochemical analysis or, again, antibody testing to determine whether they are involved. Therein lies the rub. Not everyone responds with what we might call an "appropriate" response (one that we can detect readily). We just have to know that these lectins can and *do* cause changes in the individual cells of the body (neurons, nephrons, blood cells, etc.) of susceptible individuals. I contend that the "big 4"—gluten (from wheat, barley, rye), dairy, soy and corn—are not healthy for anyone. They are simply better tolerated by some than others. This is the nature of "spectrum disorders" among individuals, who range in affliction from the "best of the best" to the "worst of the worst." Once again, thinking "peanut allergy" helps us to envision the "worst of the worst." Now that's a sensitivity!

For the sake of previous discussions on the dietary aspects of epilepsy, does gluten affect neurons? It definitely can. Can gluten *kill* neurons? Yes, indeed! If an inquiring individual were to do an Internet search for "gluten, neurons," they would find some very relevant articles. How the lectins of gluten damage and kill neurons is the interesting thing, and the answer lies in understanding of the mechanisms of cellular physiology and how that cell responds to challenges. A concurrent study of viruses helps to complete the big picture and that is why I write so much about this on my site now.

It is logical that the viruses *inside that cell* are among the things that determine the response of that cell to the challenge by lectins, carcinogens, and other chemicals/pollutants/preservatives, etc. It has been described in the literature that a cell can have as many as ten different responses to a lectin challenge, ranging from cell death (apoptosis) to tumor formation. I believe that one of the answers lies in the adaptive viruses found inside that cell. After all, that is what viruses do in nature—they facilitate adaptation (as well as cause variation in nature).

The phenomenal thing is that our very DNA contains these adaptive viruses. Researchers now estimate that up to 45% of the genetic codes in our double stranded DNA are actually viral information, some active and some extinct. This is what retroviruses, in particular, do. They infect the cell and incorporate their genetic information into our DNA. That is why these particular viruses are involved in cancer and why cancer *can* be "genetic" (inherited). This “genetic” information can then be transmitted vertically to offspring.

As heretical as it may seem, I am now convinced that cancer itself is an adaptive process. The viruses that "cause" cancer are simply adapting to the challenges (eg, carcinogens) that we keep throwing at them. When all else fails, they cause the cell that they are designed to protect to start growing out of control in order to ensure the survival of that virus and the cell itself. Thus, I now view a tumor as a “protective cocoon.” Is this a radical idea? Yes, it is. Does it make sense once it is understood that viruses are vital to the normal function of plants and animals (including humans) and that their main purpose is to facilitate adaptation? It certainly does to me.

So why don't we all have cancer and develop it early in our lives? Once again, because there is another part of the "syndrome" that is necessary—a weakened immune system. That’s right. We are all killing cancer cells right now (hopefully). The immune system recognizes when a cell is trying to do something inappropriate or harmful and sends in the cavalry. This could be just what we (incorrectly) label as an "autoimmune response." Once again, I contend that the body *does* know exactly what it is doing each and every time it does something. Again, we just don't understand what it is doing sometimes and I believe that what we call “autoimmune disease” is one of those times.

How does this apply to epilepsy and other neurodegenerative diseases such as multiple sclerosis, Alzheimer's, Parkinson's, and ALS? As stated above, some viruses have a distinct affinity for the central nervous system. The two most common brain tumors in veterinary medicine are the oligodendroglioma and astrocytoma, both of which are likely to be viral neoplasms involving those cells that control many of the supportive functions of the neuron, including the production of the myelin sheath and the control of neurotransmitter levels (glutamate). If there are viruses in those cells causing tumors, then through "reverse engineering" we can see that there are going to be the processes (eg, "autoimmune diseases") taking place that precede the formation of these tumors because these are the means by which the immune system controls the tumor production...until it is overwhelmed by all the toxins we are throwing at it.

Latent viruses are involved in many of the disease "syndromes" with which we are afflicted, including epilepsy and cancer. I like to use cancer as the parallel to illustrate the difference between "causes" and "triggers." For example, carcinogens do not “cause” cancer. Viruses are the principle, *proven* cause of cancer (eg, retroviruses). Carcinogens simply incite the virus into causing that cancer. I am convinced that the public will be told in the (near) future that all cancer is viral. Researchers have been saying this for years and years. After all, it is what some viruses do, incorporating their DNA into that of the host only to have that cell reproduce out of control at a later date. It is those ugly chemicals and pollutants we call carcinogens that trigger those viruses into turning the DNA into a cell factory.

But, viruses and carcinogens alone are not sufficient for the individual to develop cancer. The host must also experience some degree of immune failure in order to get the "big C." So, it is this triad of factors...viruses, carcinogens, and immune failure...that come together to yield the resulting cancer. That is what we call a "syndrome."

Epilepsy is also a syndrome and the parallel is probably already quite clear. Most individuals are loaded with viruses that have the potential to cause seizures. In humans, Epstein-Barr (EBV) is one such Herpes virus; 50% of our children in the US have Epstein-Barr by age 5 and 95% of Americans over age 40 have this virus in their body. Many epilepsy sufferers have not ever been told that viruses are known causes of seizures. The fact is that there are over 25 viruses *known* to causes seizures in people, many of which are ubiquitous, including Epstein-Barr, Herpes simplex, measles, mumps, Coxsackie viruses, and many more). Of course, measles and mumps are in the paramyxovirus group, to which the virus of canine distemper belongs.

But why don't all humans have seizures if EBV can cause them? One explanation would be that most individuals don't have the right cofactors in place to make it happen. And there are many cofactors in epilepsy: Diet, the existence of food intolerance (eg, celiac disease), air quality, hormonal influences, lifestyles, and many other things that affect the immune system as well as the health of the central nervous system, liver, kidneys, and endocrine systems, all of which can play vital roles.

Of all of these factors, diet is clearly the most important. This is very easy to see once we understand what is required of our brains, bodies, and immune systems in order to stay healthy and operate optimally. The "big 4" (gluten, dairy, soy, and corn) are the “who's who" of what is wrong with foods, as they damage our gut's ability to absorb nutrients (eg, celiac disease), shower our body with damaging proteins (lectins), load us up with staggering levels of "excitotoxins" (glutamate and aspartate), and pound us with estrogens. As a result, tissue health suffers, immunity fails, enzyme systems go down, and the Pandora's box of viruses is opened wide.

Many of the viral infections acquired by humans and pets during their lifetime do not come and go but rather come and *stay*. As I am fond of saying, "If I could do a Star Trek type of scan on your body and give you a print out of the viruses you have in there, once you got over the shock of that news, you might just be motivated to take better care of yourself, eh?" Some infections are "diphasic," with the initial infection causing some signs while other symptoms arise later once the individual fails to control the initial infection or continues to bombard these viruses in situ with things that "make them mad."

A number of these viruses have an affinity for the glial cells (astrocytes and oligodendrocytes) that support the neuron and regulate the levels of neurotransmitters (eg, glutamate) at the synapse. I contend that this is one of the main reasons why "the G.A.R.D" (the glutamate/aspartate restricted diet) works so well to help control seizures, as it dramatically reduces the work load of these dysfunctional cells and puts a great Band Aid on the epilepsy situation. But, the long-term solution comes from the very same diet (also called the gut absorption recovery diet), which helps to reverse the malabsorption/malnutrition syndrome that ushered in immune failure and tissue ill health that set the stage for the viral uprising.

The bottom line is that viruses don't like certain things hurled at them (eg, lectins, chemicals, and pollution). Their first reaction is one of adaptation, enabling the target cell to function in the presence of the offending agent. For example, I believe that seizures actually serve a purpose by effectively disposing of the excess glutamate that could otherwise kill the neuron. Glutamate is not only neurostimulating but potentially neurolethal, as illustrated by the fact that brain death results from the "glutamate cascade" regardless of the cause of bodily death.

However, when viruses are called upon to repeatedly react to these noxious stimuli, a more involved form of adaptation is employed and one that draws the attention of the immune system. At this point, the individual had better hope that there is a competent immune system present to put down this "rebellion." If not, that candidate may suffer the full blown syndrome, whether it be "refractory" epilepsy, cancer, or that myriad of things researchers love to call "autoimmune disorders." These things are not as "idiopathic" as we have all been led to believe.

Our medical histories all line up with this once the role (and ultimate *purpose*) of viruses in nature and our bodies is grasped. They are not the malicious entities that we have labeled them to be. They are simply doing their job. The noxious stimuli being thrown at them is the real issue. We are literally *forcing* them into becoming pathogens. In addition to the plethora of obvious offending agents being imbibed, most individuals are compounding matters through poor nutrition, polluted environments, fast-paced lifestyles, and lack of sleep. All of these things add up to self-induced misery.

Our pets may not be out partying all night but the two most important—their horrific commercial diets and polluted environments—are wreaking havoc of their health. Is it really their "genetic makeup" that is cutting their lives so woefully short? Do "genes" ultimately turn on all of us? If so, why do they wait years to make that turn? If something is genetic, why does it take 10, 40 or 80 years to show up? What is waiting? Why does it wait? What brings it out of hiding? I have suggested many times that, when reading a paper on genetics, the word "gene" be replaced with the word "virus" to see if that treatise makes more sense. Suddenly, answers to the above questions start coming. Coupled with the knowledge of viral stimulants (eg, carcinogens, lectins, and other viruses), we can start to see what…or who…the real culprit is.

As the cartoon character Pogo so wisely stated years ago, "We have met the enemy…and he is *us*."

IDIOPATHIC EPILEPSY— THE DIETARY SOLUTION

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One of the earliest and most dramatic findings in my seven years of research into these food-related issues was the phenomenal response to elimination diets in those suffering from idiopathic epilepsy. In my initial study of celiac disease, I came across accounts of epileptic children with gluten intolerance showing significant improvements when placed on gluten-free diets. As most epilepsy in pets is considered "idiopathic" in the veterinary literature, this caught my attention. I also read that MSG (monosodium glutamate) and aspartame had been identified as seizure triggers in children with epilepsy. It did not take long for me to see that gluten was absolutely loaded with the parent non-essential, neurostimulating amino acids glutamate (glutamic acid) and aspartate (aspartic acid). "Could it be that simple?" I asked myself. "Could the brain be too unhealthy in some individuals to handle these amino acids in common foods? Could the "bound" forms in those food sources do to those individuals what the "free" and concentrated forms found in common food additives do?" I came across the work of Dr. Russell Blaylock (*Excitotoxins – The Taste That Kills*) in which he clearly states that MSG and aspartame have been linked to numerous neurological conditions, including migraines, epilepsy, and neurodegenerative diseases. "But could the bound forms in food really do the exact same thing?" was my question.

This seemingly novel question was quickly answered with a resounding "Yes!" The very first epileptic dog I put on a gluten-free diet stopped seizing within 48 hours. Surpassing my newfound expectations, every single case of idiopathic epilepsy (and even some cases of brain tumors) that I put on a gluten-free diet had a significant response. And with a little more research, I was able to determine what was required to completely halt the seizures in those that did not respond as well as I had come to expect. There were a number of other culprits to be identified—namely, casein, soy, and corn—as well as other foods rich in these two amino acids. But what do these phenomenal responses say about the true cause of idiopathic epilepsy?

Well, what do we know about epilepsy? It is the most common neurologic condition worldwide. This is also true in dogs. 50 million people are afflicted with epilepsy at any given time. In humans, epilepsy typically strikes between 2 and 14 years and then again after 65. Seizures usually start in the dog between 6 months and 6 years. The age of onset and the fact that developing countries have a much higher incidence than developed ones suggest an "opportunistic" disease state to me, one that preys upon an immature or inefficient immune system. And yet, the majority of epileptic cases are still classified as "idiopathic."

Fact: There are over 20 viruses that have been shown to cause seizures in people, including many that are ubiquitous and known to have latent states, with Epstein-Barr, other herpes viruses, influenza, Coxsackie, measles, and mumps being among them. Now I do not plan to turn this into a virology lecture but will simply state that I am personally of the opinion that chronic latent viruses which have an affinity for glial cells are the main underlying cause of idiopathic epilepsy. My website goes into great detail as to why I am convinced of this.

So, if viruses are the true cause of idiopathic epilepsy, where do the "big 4" foods come into the picture? One of the key points that my research revealed is that the "big 4" (gluten, casein, soy, and corn) are the main foods that induce villous atrophy of the duodenum, the principal lesion found in celiac disease. This is a crucial fact to grasp because that particular area of bowel has the vital role of absorbing many essential nutrients, including calcium, iron, iodine, B complex, vitamin C, zinc, copper, magnesium, and much more.

How hard is it to imagine the far-reaching and potentially devastating effects of the villous damage induced by these foods? In fact, there is no tissue or bodily function that does not depend on these nutrients for optimal performance. The brain, liver, immune system, and every other organ and enzyme system could suffer when this sort of chronic malabsorption takes place. And the celiac experiences it all. That is why I often refer to the duodenum as "Pandora's box"—damage it and we unleash the plagues that await us.

And, why these are the main four foods that damage this area is equally fascinating. These are the only four foods that we consume from which adhesives are made, with gluten and casein being used to make industrial glues and bases for paint. Casein, which makes up 80% of the protein fraction of cow's milk, is the protein from which Borden makes Elmer's glue. As most of you know, powerful super-glues are made from soy with which much of your car is assembled. But the best they can do with corn adhesives is to put cardboard boxes together with it. And in examining these four foods, it is interesting to note that corn is the best tolerated.

A good example of a secondary problem resulting from this villous damage is reduced serotonin production. 98% of the body's serotonin is produced by the enterochromaffin cells that line that same area of gut that is damaged by the "big 4." The other 2% is produced by the brain itself from tryptophan. However, in both areas, B complex is utilized as a coenzyme to make that conversion. But where is that B complex absorbed again? Yes, B complex is absorbed primarily by the duodenum. Thank Goodness some is absorbed sublingually. And serotonin is not only a mood moderator but plays a role in moderating the neurostimulating effects of glutamate at the synapse. I certainly believe that serotonin deficiencies play a vital role in the severity of epilepsy. Celiacs are notoriously low in this vital hormone, as illustrated by their depression, bleeding tendencies, high rates of epilepsy, and severe immune-mediated diseases.

The fascinating thing to see is that these four gut-damaging foods are also the leading dietary sources of the non-essential, neurostimulating amino acids, glutamate and aspartate. They are also rich in tissue-damaging lectins, food allergens, and estrogens. I've come to understand that this is no coincidence. "Lectin" is the term given to antibody-sized glycoproteins that occur in nature, being derived from foods, bacteria, and even our own cells. For example, the oligodendrocytes in our brain are capable of producing two different lectins, one that supports the neuron and one that can kill the neuron it serves.

The lectins that pertain to this discussion are those derived from foods and the astute reader already suspects that the main players are those derived from the "big 4": Gluten grains, dairy products, soy, and corn. All complex cells have glycoprotein receptors on their outer cell wall, to which "dock" things like antibodies, viruses, and lectins. When a lectin docks to a receptor, any one of ten different reactions can take place, from cell death to tumor formation. In between are inflammatory reactions, the production of hormones, and changes in the cell wall. Dr. D'Adamo based his eating-for-your-blood-type work on lectins, noting that certain blood types were more prone than others to the different glycoproteins of dairy, wheat, soy, and corn.

On that note, how *does* a cell know which is the appropriate response to this non-living entity? I contend that it is the *viruses* in that cell that determine the response. These viruses can force that cell to adapt or they can make that cell grow out of control, which we call tumor formation, a process that I believe is the viruses' ultimate adaptation. The role of lectins helps to explain much about the celiac's medical history, including their staggering rates of immune-mediated diseases and certain cancers.

So once again, we see that the foods that are unhealthy for us are so in numerous ways and are practically screaming out to us to stop eating them, often beginning in childhood with colic, congestion, asthma and other allergies. As I mentioned in my first article, I found a study a few years ago that found our children who get cow's milk in the first five days of life had a 40 to 50 times higher rate of asthma, type 2 diabetes, and juvenile onset rheumatoid arthritis. My study of lectins certainly supported this and I recommend everyone learn as much about these antibody-sized glycoproteins as possible. And the allergies to these foods are primarily formed at the time the damage to the gut takes place as a prelude to the showering of the body with these damaging lectins, which have their hand in a wide range of immune-mediated disorders. The estrogens these foods contain add significantly to the problem, as estrogens are both inflammatory and immune suppressive.

But for the topic of epilepsy, I will focus on the glutamate content. The foods richest in glutamate are the gluten grains (wheat, barley, and rye), dairy products, beans and legumes (especially soy and peanuts), nuts and seeds, and foods prepared with the "free" form known as MSG. Meats are also rich in glutamate content but alone do not do any intestinal harm. It is the combination of the villous atrophy, damage to the cells that covert glutamate to glutamine, and the rich glutamate content of the "big 4" that distinguish them as the main culprits.

I *have* done my homework, finding sites that list the glutamate and aspartate content of common foods and making tables and charts to give to interested parties, mainly to illustrate the fact that the main food allergens are also the culprits here, while the universally healthy food-namely fruits and veggie- are lowest in these non-essential amino acids. Some things do make sense.

As I mentioned, I have been treating epileptic veterinary patients for several years employing a glutamate/aspartate-restricted diet (now known as "The G.A.R.D.") with phenomenal success. In fact, I have yet to have a case that did not show significant improvement, most of which stopped seizing within 48 hours and only had recurrences when the owners were non-compliant. My (free) Internet consultations during those years have generated some fascinating human testimonials by those who have applied these principles on their own. Both children and adults have responded dramatically, just as my early study about celiac epileptics suggested.

One extremely important personal discovery was a seizure pattern of the un-medicated epileptic dog, which showed that the typical interval between eating a high glutamate meal and having a seizure was 4 to 6 hours (as opposed to a 30 minutes to an hour interval seen when people ingested the "free" forms, MSG and aspartame.) This 6-hour lag time is consistent with the effects these same foods have on the human "insomniac," who eats dinner and dessert at 7 to 8 PM and awakens each night at 1 to 2 AM. The parallels are obvious.

By applying The G.A.R.D., we put an immediate Band-Aid on the situation by dramatically reducing the glutamate load on the diseased neurons, liver, and intestinal cells. This has halted seizures, literally overnight, in otherwise refractory seizure patients. Again, I cannot over-stress how well this has worked. But the long-term recovery of the epileptic comes from the same restrictive dietary approach, as it allows the gut to heal and function better. This includes the return to proper nutrient absorption as well as the production of serotonin and melatonin, two hormones that are vital to our health, especially to that of the central nervous system. That is why I now also refer to The G.A.R.D. as the "gut absorption recovery diet."

Of course, epilepsy is not the only neurologic disorder that is affected by the downward spiral created by these trouble foods. The "excitotoxins" are vitally involved in ADHD, migraines, pain syndromes (eg, fibromyalgia) and neurodegenerative diseases such as ALS and Alzheimer's. Again, Dr. Blaylock has pioneered much of this work. Now imagine the brains of those individuals with food intolerance that have been afflicted by nutrient malabsorption their entire life. Then, throw in the deleterious effects of fast food, hydrogenated oils, and polluted environments while folding in our fast-paced lifestyles, lack of restorative sleep, and overuse of symptomatic medication and we have a recipe for disaster. Our current medical dilemma really should be no mystery at all.

And the *real* problems begin in "Pandora's box." The "Big 4" are the "Who's Who" of unhealthy foods and celiacs are the "martyrs," showing the world just how bad things can get when we eat something that our body no longer wants. In the sensitized individual, these foods can induce villous atrophy with the resultant malabsorption syndrome compromising the entire body including the brain, liver, and immune system. They also cause the release of histamine, which increases the permeability of the blood brain barrier thereby allowing more of the excitotoxins into the brain. Furthermore, these foods are loaded with those harmful lectins on which Dr. D'Adamo has written volumes of great information. And last but not least, the gluten grains, dairy and soy are also suppliers of medically significant amounts of dietary estrogens, which can be both chronically inflammatory and immune suppressive—a deadly combination when viruses are in play. Their role in breast cancer is well established.

The "four horsemen" are wreaking havoc on countless lives and now we know exactly why. They are particularly nasty when it comes to neurologic conditions, ranging from simple depression/chronic fatigue to severe neurodegenerative disorders. Their bombardment of the brain with lectins and excitotoxins (once the brain has become adequately diseased) clearly precipitates the seizures seen in idiopathic epilepsy. I now view epilepsy as a "syndrome" but these trouble foods have their hand in multiple aspects of that syndrome. And *dramatic* recoveries can occur when the "Big 4" are eliminated from the diets of afflicted individuals. However, epilepsy is just "the hook" as I like to term it. It is simply a glaring example of the vast array of conditions in which food intolerance has its hands.

It has become painfully clear to me that a proper diet has more potential to prevent and treat disease- as well as extend life expectancy—than anything else under our immediate control. Once again, we do have our health destinies in our own hands.

PROLOTHERAPY – A SIMPLE, NATURAL TECHNIQUE THAT STIMULATES THE BODY TO REPAIR DAMAGED/LOOSE LIGAMENTS

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HISTORY

Prolotherapy (sometimes known as *regenerative injection therapy* and more inaccurately as *sclerotherapy*) is not new. The concept of irritating tissue to promote healing dates as far back as the ancient Greeks and our old friend Hippocrates, who treated Olympic javelin throwers with unstable shoulders by touching with what he described as a "slender hot iron" to the ligaments holding the shoulder joint together. The heat would irritate the ligament capsule, causing it to tighten up.

Prolotherapy was used in France to treat hernias before modern surgical techniques became available.

The techniques we use today were developed in the 1930s by G.S. Hackett, MD, a surgeon from Ohio, along with other MDs and DOs. The same techniques subsequently have been used successfully for pain relief from ligament laxity for nearly 60 years.

Hackett coined the term "prolotherapy" because his initial work demonstrated that the new tissue laid down during the healing process was new healthy tissue, not scar tissue. (This distinguishes prolotherapy from a related treatment known as "sclerotherapy.") "Prolo-" stands for proliferative, implying that new cells and collagen fibers are proliferating and growing. The term "regenerative injection therapy" which is now being used by some practitioners is fairly new and is an attempt to portray more accurately what is actually taking place physiologically.

VETERINARY HISTORY

For years pin-firing and blistering in horses (oddly enough called counter-irritants) were commonly used techniques. They were essentially a type of prolotherapy. They have fallen into disrepute, and while I'm not an equine practitioner, I suspect that prolotherapy in selected cases would be a useful technique in horses.

A short paper entitled "Electrosurgical Treatment for Cranial Cruciate Ligament Rupture" was published in the June 1979 VM/SAC in their clinical briefs section. Since it is such a short piece I have reproduced it in entirety:

> Two prevalent methods for dealing with cranial cruciate ligament rupture in dogs are reconstruction and imbrication. Both are involved and expensive procedures. Electrosurgery is a simple alternative and does not obviate a surgical approach.
>
> With the dog under thiamylal sodium anesthesia, the stifle area is prepared aseptically, and a 1/32"x 3/4" straight needle (Cameron Miller) is applied to the skin, down to the periosteum, in a line-firing pattern at points 1/2" apart, from the humeral epicondyles to the tibial condyles. Five to six holes usually suffice in each of 4 lines: 1 each craniad to the lateral and medial collateral ligaments, respectively, and 2 over the cranial aspect of the stifle (Figure 1).
>
> This procedure produces an *acute inflammation, resolution of which results in functional stability of the joint within a week*. In 6 of 94 cases the procedure had to be repeated, but none has required surgery after electrocautery.

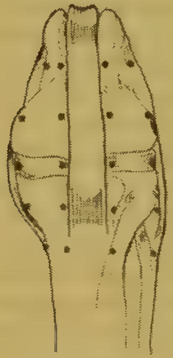

Figure 1.

SCIENTIFIC EVIDENCE

Hackett was the first to demonstrate clinically and scientifically a method of strengthening ligaments, and was the first to coin the word *prolotherapy*. He showed that by creating controlled inflammation permanent increases in ligaments size (35% to 40%) resulted. He reported an 82% patient-reported cure rate of backache in a series of 1,600 patients treated with prolotherapy. His final examinations were performed from 2 to 12 years following the conclusion of injection therapy, thus indicating the permanency of the treatment.

More recent studies have confirmed his initial studies. In 1983, Liu et al. injected a proliferative solution (aodium morrhuate) into rabbit medial collateral ligaments (MCLs) of the knee. The ligaments showed a significant increase in ligament mass, thickness, ligament-bone junction strength and weight-to-length ratio compared to controls. This effect was confirmed by Maynard et al in 1985 in his study on Achilles tendons in rabbits. In a human study in 1989, Klein et al. documented cellular evidence of new collagen growth when comparing pre- and postinjection sacroiliac ligament.

PHYSIOLOGY

In a sense, prolotherapy creates an injury. Figure 2 shows schematically what happens during healing. Cellular debris and humoral factors at the injury site attract an initial influx of granulocytes. The granulocytes proceed to secrete a number of factors, among them proteolytic enzymes, which debride to wound area and attract other cells. Ultimately fibroblasts are recruited and are stimulated to produce new intracellular matrix, including new collagen. As this collagen is produced it creates tissue remodeling and strengthening of the area, including the wound contraction we see in Figure 2. This contraction of the wound as a result of the production of new collagen/ligaments creates a tightening of the wound, and reduction in joint laxity and therefore the reduction in pain. The whole process is called the *wound healing cascade*, and, in the very basic model that is very briefly described above, is characteristic of all healing wounds.

THOUGHTS ON OTHER ASPECTS OF THE RATIONALE FOR THE THERAPY

A number of years ago Sharon Willoughby, DVM, DC posited that a major reason for the spinal arthritis that we see in big dogs was to some level of joint laxity in the articular facets of the vertebrae. This led to the body's only response to an appropriate function – inflammation.

A series of articles by Kealy et al In JAVMA reported on 48 Labrador retrievers in a long-term split-litter study where one dog in each pair was fed 25% less food than its pair mate from 8 weeks of age until death. In the limited fed dogs there was significantly less (75% less at the five year mark) arthritis than in the full fed group. In a recent conversation with one of the authors I was told there will be further papers generated by this long-term study looking at various orthopedic aspects of the study. Could it be that growing slowly allowed the ligaments to grow appropriately along with the bones and muscles?

A recent paper by K. Dean Reeves, MD, and Khatab M. Hassenein, PhD (*Alternative Therapies* May/June 2003) entitled "Long Term Effects of Dextrose Prolotherapy for Anterior Cruciate Ligament Laxity" has a title that tells most of the story.

TECHNIQUE

This is one of the simplest therapies that you can use. Prolotherapy (which I had first heard about in the 1980s) had sat on the shelf until a number of years ago since I was having good luck with the electrosurgery procedure mentioned above. Through a variety of personal medical issues the therapy came off the shelf and I began to explore it for myself. When I reached a physiatrist (MD pain management specialist) his first comment to me was "You're a vet–do it to your self. I'm 80 miles away from you." I did find someone closer that did some work with me as a patient. He also became to some degree a mentor, giving me books and pointers. The whole experience got me started with the procedure.

To be successful with prolotherapy, it is critical that **you know your anatomy**. It will not be effective if you don't get the solution where it needs to be—that is, into the ligament and at the boney interface of the ligament.

In our practice we use 15% dextrose as our predominant injection solution into the ligaments, and 25% into the joint (see Figure 2).

References are available from the author upon request.

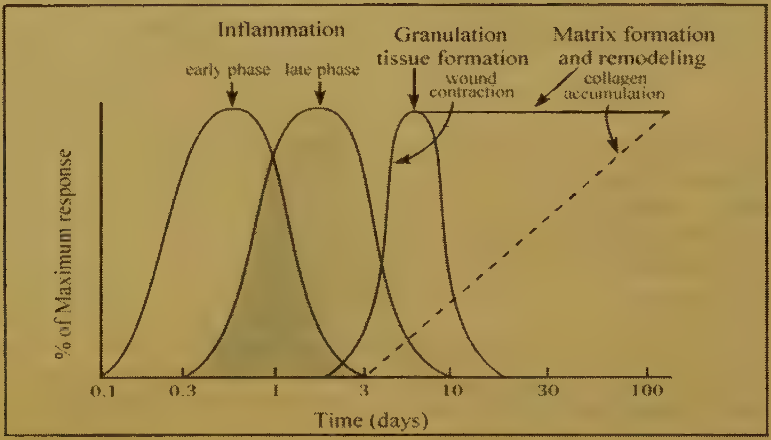

Figure 2. The wound healing cascade.

ANESTHETIC COMPLICATIONS

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Many anesthetic drugs decrease cardiac output (CO), blood pressure (BP), heart rate (HR), tidal volume (TV), respiratory rate (RR), and body temperature (BT) regulation. Complications arising from the surgical procedure itself may result in further depression of CO and ventilation. The early sympathetic nervous system (SNS) reactivity to hypoxemia, hypercarbia, hypotension, and reduced tissue perfusion is reduced under anesthesia, and there is limited ability to compensate. Monitoring of oxygenation, ventilation, and arterial blood pressure are critical, as impairment of the cardiovascular and pulmonary systems can rapidly result in cardiac arrest.

RESPIRATORY COMPLICATIONS (See Table 1)

General Effects of Anesthesia on the Respiratory System

- V/Q (alveolar ventilation to perfusion ratio) mismatch, due to alveolar hypoventilation, reduced pulmonary perfusion, and shunting of pulmonary blood, is common.
- Functional residual capacity (FRC) is reduced, particularly with the patient in dorsal recumbency.
- When FRC is close to or less than the closing volume of the lung, the small airways close, resulting in atelectasis, right to left shunting of blood in the pulmonary vasculature, and hypoxemia.
- Brainstem respiratory centers are depressed by general anesthetics and mu agonist opioids, resulting in a shift in the CO_2 response curve and reduced hypoxic respiratory drive.
- Reduced compliance and increased resistance of the thorax and lungs results in a change to a diaphragmatic breathing pattern.
- Cilial paralysis, mucosal drying, and depressed airway protective reflexes also impair respiratory function.

Hypoxemia

- One of the most immediately life-threatening complications that occur under anesthesia is hypoxemia.
- Hypoxemia is identified from an O_2 saturation (SaO_2) <90%, or a PaO_2 < 60 mmHg.
- Mild arterial hypoxemia (PaO_2 < 60 mmHg; < 8 kPa; SaO_2 <90%) causes activation of the SNS.
  - Early clinical signs include restlessness, dysphoria, tachycardia, dysrhythmias, and hypertension.
  - Hypoxemia initially causes stimulation of respiration and increased minute ventilation
  - Cheyne-Stokes breathing pattern may be observed.
  - HR, stroke volume (SV), myocardial contractility, and CO increase.
  - Systemic vascular resistance (SVR) increases and mild hypertension may occur.
- With moderate arterial hypoxemia, (SaO_2 60–80%), local vasodilation may predominate and SVR and BP decrease.
  - HR may continue to increase because of the baroreceptor reflex response.
- With severe hypoxemia (SaO_2 < 60%), local depressant effects predominate and BP falls rapidly, the HR slows, shock develops, and ventricular fibrillation or asystole follow.
  - Inadequate supply of oxygen to the brain stem results in hypoventilation and apnea.
  - CNS depression, bradycardia, hypotension, and cardiac arrest are terminal signs.
- Hypoxemia promotes cardiac arrhythmias (usually ventricular), due to a decreased myocardial O_2 supply-demand ratio.

Airway Obstruction

- With obstructed airways, animals ventilate to minimize the resistance work of breathing, resulting in a reduced RR and increased TV to maintain minute ventilation.
- Many anesthetic drugs cause increased relaxation of pharyngeal tissues, causing further obstruction.

Upper Airway Obstruction (Inspiratory Dyspnea)

- Partial obstruction results in inspiratory stridor with slow, deep breaths. Paradoxical breathing may be observed.
- Full obstruction results in pronounced paradoxical breathing and hyperextension of head and neck. No inspiratory stridor may be heard.
- The upper airway may undergo a dynamic inspiratory compression.
- Pulmonary edema and acute lung injury can result.

Lower Airway Obstruction (Expiratory Dyspnea)

Restrictive Pulmonary Disease:

- Decreased lung compliance and increased lung elastance can result from restrictive diseases extrinsic (ie, pneumothorax) or intrinsic (ie, pneumonia) to the lungs.
- Restrictive pulmonary diseases result in the lungs collapsing and becoming less compliant.
- This increases the work of breathing to overcome the elastic forces and expand the lungs, and a rapid shallow breathing pattern is adopted.

Hypoventilation/Hypercapnia (reduced minute ventilation: reduced TV and/or RR)

- End-tidal (ET) CO_2 or $PaCO_2$ > 45 mmHg (6 kPa) is indicative of hypoventilation.
- Patients receiving 100% oxygen under anesthesia are less likely to become hypoxemic during hypoventilation, but patients that are on room air (21% FIO_2) will.

- Hypercapnia impairs oxygenation by displacing oxygen in the alveolus with the high concentrations of CO_2, resulting in decreased alveolar and arterial oxygen concentration.
- Hypercapnia causes direct depression of cardiac and vascular smooth muscle and reflex stimulation of the SNS.
- Mild hypercapnia ($PaCO_2$ 45-60 mmHg) results in mild SNS stimulation, tachycardia, mild hypertension, stimulation of respiration and an increase in minute ventilation
- With moderate to severe hypercapnia ($PaCO_2$ 60-85 mmHg), SNS stimulation first results in tachycardia and hypertension, increasing myocardial O_2 demand, and later results in decreased myocardial O_2 supply, due to tachycardia and hypotension. CNS depression occurs.
- With severe hypercapnia ($PaCO_2$ > 90 mmHg), severe CNS depression occurs, respiratory stimulation is reduced, and apnea occurs.
- Hypercapnia can also cause ventricular arrhythmias.

CARDIOVASCULAR COMPLICATIONS (See Table 2)

General Effects of Anesthesia on the Cardiovascular System

- Many anesthetics (volatile and injectable) produce a dose-related:
  - Depression of left ventricular (LV), right ventricular (RV), and left atrial (LA) myocardial contractility (negative inotropy) by altering intracellular Ca^{2+} homeostasis.
  - Decrease in LV diastolic function (negative lusitropy).
  - Decrease in LV afterload due to vasodilation and a reduction in SVR.
  - Depression of baroreceptor reflex control of BP.
- These effects result in reduced venous return, hypotension, bradycardia, and a decrease in CO, and are exacerbated in a failing heart.

Cardiac Dysrhythmias

- Bradydysrhythmias
  - Severe bradydysrhythmias can greatly reduce CO, BP, and tissue perfusion if there is limited ability to increase contractility or increase venous return by vasoconstriction.
- Atrial Tachydysrhythmias:
  - Severe tachydysrhythmias reduce CO and tissue perfusion due to decreased time for diastolic filling, reduced ejection time, reduced time for coronary perfusion, and myocardial ischemia.
- Ventricular Dysrhythmias
  - Common types of ventricular dysrhythmias seen under anesthesia include PVCs, ventricular tachycardia, and ventricular fibrillation and can dramatically decrease CO.

Hypotension

- Pathophysiology of hypotension:
  - BP is the force driving tissue perfusion, and a MAP of at least 60 mmHg and an SAP of at least 80 mmHg is necessary for perfusion of the brain, heart, and kidneys.
  - Adequate BP does not always indicate adequate CO and tissue perfusion; significant vasoconstriction will result in a high BP, but CO and tissue perfusion may be low.
  - Hypoperfusion of vital organs and the extremities results in inadequate tissue delivery of oxygen and removal of waste products, and clinical signs of shock and subsequent organ dysfunction.
- Treatment of Hypotension:
  - Reduce amount of injectable or inhalational anesthetic by administering additional analgesics with MAC-sparing effects (mu-agonist opioids, ketamine, lidocaine).
  - Bolus IV administration of 20–30 mL/kg of balanced, isotonic, crystalloid solution (attempt 1–2 times), or 5–20 mL/kg of colloid solution (maximum 20 mL/kg/24 hr) to increase intravascular volume (if no underlying cardiac disease or oliguric or anuric renal failure).
  - Correct hypoxemia, hypercapnia, acid–base, and electrolyte disturbances.
  - Provide sympathomimetic support–anticholinergics, vasoconstrictors, and positive inotropes.

Hypertension

- Arterial BP is the most important determinant of left ventricular afterload and cardiac work.
- Hypertension (MAP > 100 mmHg and SAP >160 mmHg) results in increased myocardial work and increased myocardial oxygen demand, which could result in myocardial ischemia and cardiac dysrhythmias.
- Hypertension can result in retinopathy, blindness, and renal failure.
- Sudden hypertension during anesthesia indicates SNS stimulation, and possible causes must be ruled out.

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Table 1. Common Respiratory Complications of General Anesthesia

Clinical Sign	Etiology	Rule-outs	Treatment
Dyspnea: **Obstructive Pulmonary Disease**	Upper airway (inspiratory dyspnea)	Brachycephalics Soft palate entrapment Laryngeal or tracheal obstruction Laryngeal paralysis Head bandage too tight Kinked ET tube	Oxygen Extend head and neck and pull tongue forward Suction airway Endotracheal intubation Steroids and diuretics +/- sedation
	Lower airway (expiratory dyspnea)	Bronchospasm Asthma, COPD Anaphylaxis	Oxygen Bronchodilator Steroids, Antihistamines
Restrictive Pulmonary Disease (rapid, shallow breaths)	**Intrinsic:** **Extrinsic**	Pulmonary edema, pneumonia, infiltrates, ARDS Pneumothorax, pleural effusion, increased intra-abdominal pressure	Oxygen Thoracocentesis Endotracheal intubation IPPV Alveolar recruitment maneuver
Hypoxia	V/Q mismatch and right to left intrapulmonary shunting	Apnea/hypoventilation Atelectasis Inadequate FiO_2 Airway obstruction Restrictive lung disease Severe anemia Severe hypotension Cardiac arrest	Oxygen Endotracheal (ET) intubation and IPPV Alveolar recruitment maneuver Reversal of CNS depressant drugs Thoracocentesis Bronchodilators, Diuretics Hemoglobin transfusion Sympathomimetic support +/- CPR
Hypoventilation	Reduced FRC Reduced minute ventilation (RR or TV)	Positioning Relaxation of respiratory muscles Resp. depressant drugs Abdominal distension Hypotension, Hypothermia Airway obstruction	ET intubation IPPV Reverse respiratory depressant drugs if effects are severe Reduce abdominal distension Correct hypotension, hypothermia Correct airway obstruction
Respiratory Arrest	Depression of brainstem respiratory centers	Overdosage of anesthetics Reflex apnea Brain stem injury Cardiac arrest	ET intubation IPPV CPR
Hyperventilation	Increased minute ventilation (respiratory rate and/or TV)	Inadequate depth of anesthesia Hypercapnia, hypoxemia Hyperthermia	Increase depth of anesthesia if required Check absorber granules, one-way valves, fresh gas flow, and the breathing circuit
Aspiration	Aspiration of GI contents Aspiration of blood, saliva, mucus, or pus	Drugs that lower LES tone Factors that delay gastric emptying (pain, fear, opioids) Increased intra-abdominal pressure (pregnancy, ascites, GI obstruction) Prolonged anesthesia	Appropriate fasting Rapid IV induction and control of airway in fed patients Pre- or post- treatment with prokinetic drugs, H-2 blockers, or proton pump inhibitors Position head down to allow drainage Suction and lavage of esophagus Sucralfate

Table 2. Common Cardiovascular Complications of General Anesthesia

Clinical Sign	Etiology	Treatment
Bradydysrhythmias • Sinus bradycardia • A-V block (1° or 2°) • Sinus arrest • Atrial standstill	Potent mu opioids High vagal tone Hypothermia CNS disease & increased ICP Hyperkalemia Addisonian crisis	Anticholinergic Butorphanol or naloxone to reverse mu opioid effects Warm patient Decrease ICP Correct hyperkalemia
Tachydysrhythmias • Sinus tachycardia • Atrial tachycardia • Atrial fibrillation	Drug induced (atropine) SNS stimulation: pain, hypoxemia, awareness, hyperthermia, anemia, hypotension, hypovolemia Myocardial disease	Rule out and treat underlying cause Beta blockers (esmolol or propranolol)
Ventricular dysrhythmias • Ventricular premature contractions • Ventricular tachycardia • Ventricular fibrillation	Hypoxia, myocardial ischemia, traumatic myocarditis, GDV, splenic disease, hypercapnia, acid–base imbalance, electrolyte imbalance, drug effects (thiobarbiturates)	Rule out and treat underlying cause Lidocaine, procainamide, Mexilitene Magnesium sulphate CPR
Hypotension (Bradydysrhythmias and Tachydysrhythmias can also contribute to hypotension and should be ruled out and treated)	**Decreased venous return:** • Vasodilation • Hypovolemia • IPPV • Pericardial effusion • Tension pneumothorax • Closed pop-off valve • Surgical packing and retraction of organs • Severe bradycardia	Increase intravascular volume with balanced, isotonic, crystalloid or colloid administration Thoracocentesis Pericardiocentesis Open pop-off valve Reduce surgical traction Reduce mean airway pressure and the I:E ratio with IPPV
	Vasodilation (volatile anesthetics, propofol, and thiopental cause vasodilation)	Administer a vasoconstrictor: • Dopamine • Ephedrine • Epinephrine • Vasopressin
	Ventricular dysfunction	Administer a positive inotrope: • Dobutamine • Dopamine • Ephedrine • Epinephrine
Hypertension	Pain Hypoxemia Hypercapnia Metabolic acidosis Underlying renal or cardiac disease	Rule out and treat underlying cause Beta blockers ACE inhibitors

Table 3. Emergency Drugs Used During General Anesthesia

Drug	Indications	Dose	Possible Side Effects
Atropine	Bradycardia AV block Sinus arrest Ventricular asystole	0.01–0.02 mg/kg IV	Tachycardia Central cholinergic syndrome
Aminophylline	Bronchospasm Asthma Anaphylaxis	0.2–0.6 mg/kg	Tachycardia Dysrhythmias Hypotension
Albuterol	Bronchospasm Asthma Anaphylaxis	0.15 mg/kg Inhaled	Tachycardia Dysrhythmias Hypotension
Calcium	Known hypocalcemia Calcium channel blocker overdosage	1 mL/9kg 10% CaCl 1 mL/2.3 kg Calcium gluconate	Bradycardia Dysrhythmias
Corticosteroids	Anti-inflammation Stabilization of blood vessels Analgesic	Dexamethasone: 0.5–1 mg/kg IV Methylprednisolone: 20 mg/kg IV	Infection GI or renal ischemia
Diphenhydramine	Antihistamine	2.2 mg/kg IV or IM	Hypotension if given rapidly IV
Dobutamine	Hypotension Myocardial dysfunction	2–10 μg/kg/min	Tachycardia Dysrhythmias
Dopamine	Renal failure Hypotension Myocardial dysfunction Vasodilation	2–20 μg/kg/min	Tachycardia Dysrhythmias
Ephedrine	Hypotension	0.03–0.06 mg/kg IV	Tachycardia Dysrhythmias
Epinephrine	Hypotension Refractory bradycardia Anaphylaxis CPA	0.01–0.2 mg/kg IV/IO/IT 0.01–0.03 μg/kg/min	Tachycardia Dysrhythmias
Esmolol	Beta-blocker Hypertension Tachycardia	50–200 μg/kg/min	Hypotension
Furosemide	Diuretic Pulmonary edema Cerebral edema Laryngeal edema	1–2 mg/kg IV	Excessive diuresis Hypokalemia
Glycopyrrolate	Bradycardia	0.01 mg/kg IV	Tachycardia
Isoproterenol	Refractory bradycardia Ventricular asystole	0.01–0.1 mg/kg/min	Hypotension
Lidocaine	Ventricular premature contractions Ventricular tachycardia Ventricular fibrillation	1–2 mg/kg IV 20–100 μg/kg/min	Bradycardia Hypotension Seizures
Magnesium chloride	Given with prolonged CPA or intractable Ventricular fibrillation	1–2 ml/20 kg over 10 minutes	Hypotension CNS depression
Procainamide	VPCs Ventricular tachycardia Ventricular fibrillation	10–20 mg/kg/hour	Bradycardia Hypotension Seizures
Terbutaline	Bronchospasm Asthma Anaphylaxis	0.01 mg/kg IV	Tachycardia Hypotension Dysrhythmias

Table 3. Continued.

Sodium Bicarbonate	Metabolic acidosis During CPR: • If pre-existing metabolic acidosis • >10 minutes of CPR	0.5 mEq/kg IV over 20–30 minutes Use	Metabolic alkalosis Respiratory arrest if given too quickly Hyperosmolality
Vasopressin	Vasodilatory shock (sepsis) Ventricular fibrillation unresponsive to defibrillation or epinephrine.	0.5 units/kg once	Severe vasoconstriction Dysrhythmias

LOCAL AND REGIONAL ANESTHETIC AND ANALGESIC TECHNIQUES

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- Provides more effective analgesia
- Allows the use of lower doses of drugs, resulting in fewer adverse effects
- Significant "MAC sparing" effects, allowing the use of lower concentrations of inhalant anesthetics
- Combinations of local anesthetic/opioid, local anesthetic/alpha-2 agonist, or opioid/alpha-2 agonist can provide multi-modal analgesia

DRUGS USED FOR LOCAL AND REGIONAL ANALGESIA AND ANESTHESIA

Local Anesthetic Drugs

- Block nerve conduction in all types of neurons (all pain fibers (A-delta and C fibers), motor and sympathetic neurons).
- The drug must penetrate the connective tissue sheath to reach the neuronal cell membrane, where it blocks the generation and conduction of nerve impulses by inhibiting voltage-gated sodium channels.
- Because they block all pain fiber (A-delta and C fibers) transmission, they provide excellent pre-emptive analgesia and markedly reduce MAC.
- They also block motor and sympathetic neurons and can produce hypotension and paralysis of intercostal muscles and the diaphragm, with epidural or intrathecal administration.
- Onset and duration of blockade differs by anatomical location, fiber type, and frequency of stimulation.
  - Fibers innervating more proximal regions are more superficial in the nerve bundle, so are blocked first, with more distal regions blocked later.
  - Myelinated A-delta (pain) sensory fibers are blocked first, followed by larger sensory A-beta (touch, pressure) and A-alpha (motor) fibers, with small unmyelinated C fiber (pain) blockade occurring last.
  - Neurons in damaged tissue discharge at higher rates, so are more susceptible to blockade.

Dosage and Uptake

- Absorption across mucosal, pleural, and peritoneal surfaces is rapid, with peak plasma concentrations achieved within 10 minutes and high bioavailability.
- Absorption from subcutaneous sites is slower, with lower bioavailability.
- All local anesthetics cause vasodilation, which makes absorption of the drug more rapid.
- Epinephrine may be added to slow absorption, but should never be used for blockade of distal extremities because of the potential for local tissue ischemia.
- Base dosage calculations on lean bodyweight, and always calculate total safe dose to avoid toxicity.
  - The maximum recommended dose of bupivicaine and articaine is 4 mg/kg in dogs and 2 mg/kg in cats, and of lidocaine, is 8 mg/kg in dogs and 6 mg/kg in cats.
    - Lidocaine 2% (20 mg/mL) – duration 1–1.5 hours
    - Lidocaine 2% (20 mg/mL) with epinephrine – duration 1.5–2 hours
    - Bupivacaine 0.5% (5 mg/mL) (Marcaine®) – duration 4–6 hours
    - Articaine 4% (40 mg/mL) (Septicaine®) (with epinephrine) – duration 4–6 hours

Toxicity

- Overdosage results in cardiac depression, hypotension, seizures, coma, death.
- Animals with questionable liver function should be dosed carefully, as toxic doses are lower.
- Inadvertent IV injection of bupivicaine, which is highly toxic to the cardiovascular system and CNS (decreased contractility, dysrhythmias, decreased cardiac output, hypotension, seizures, coma), can result in cardiovascular collapse; **always aspirate syringe prior to injection of any local anesthetic to avoid IV or intra-arterial injection.**
- Allergic reactions can occur, but are uncommon.
- Although all local anesthetics can cause tissue irritation, very concentrated local anesthetic solutions (lidocaine 5%) are very irritating to tissues and neurotoxic, resulting in permanent conduction blockade.

Opioids

- Block primarily C fibers, and do not block A-delta, motor or sympathetic nerve fibers
- The analgesia from opioids is less profound, but still very effective
- Morphine is often injected into joints and is used for epidural analgesia.

Incisional Line Block

- Use before surgical incision, or after surgery and before skin closure.
- Use a 25-gauge, 1-inch hypodermic needle and a syringe.
- Insert the needle subcutaneously after a sterile prep, and inject prior to incision or before complete closure.
- Aspirate prior to injection and inject along the entire incision, fanning out your injections and aspirating back as you move the needle.

- Bupivacaine (0.5%), Lidocaine (2%; with or without epinephrine), or Articaine (4%) can be used at 0.2 mL/kg or 0.1 mL/lb
- You may use a larger volume, if necessary, as long as you stay below toxic doses.

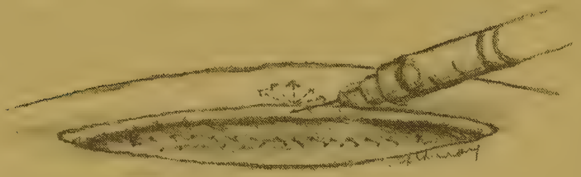

Figure 1. Incisional line block.

Intra-articular Stifle Block

- This block is used for analgesia of the joint before (pre-emptive analgesia) or after surgical intervention.
- Clip and aseptically prepare the joint
- Insert needle lateral to the patellar ligament
- Aspirate to ensure placement
- Inject drug:
  - Lidocaine, bupivicaine, or articaine (0.2 mL/kg or 0.1 mL/lb).
  - Morphine (0.1 mg/kg) can also be used alone, or in combination with a local anesthetic.
- Alternatively, this block can be place intra-operatively, after closure of the joint and before skin closure.

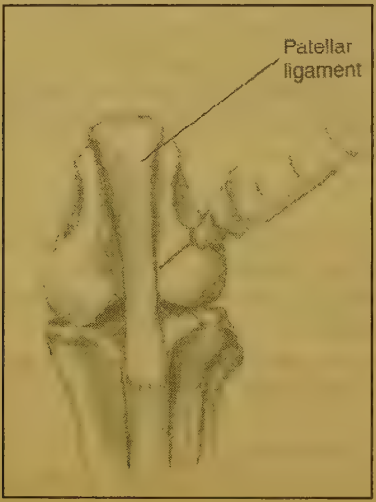

Figure 2. Intra-articular stifle block.

Brachial Plexus Nerve Blocks

Preoperative block (traditional technique):

- For surgery distal to the elbow, a brachial plexus block can be performed preoperatively to block the radial, median, ulnar, musculoskeletal and axillary nerves.
- The needle is inserted into the axillary region, medial to and at the level of the shoulder joint, directed toward the costochondral junction and parallel to the vertebral column.
- Two thirds of the dose is injected after test-aspiration, to ensure the needle is not intravascular or intrathoracic, and the remaining 1/3 is injected as the needle is withdrawn.
- The dose used is 4 mg/kg in dogs and 2 mg/kg in cats of 0.5% bupivicaine, or 8 mg/kg in dogs and 6 mg/kg in cats of 2% lidocaine solution.

Intra-operative block:

- Local anesthetic can be deposited directly around exposed nerves during forelimb amputation.
- Injecting 0.5% bupivicaine (0.2 mL/kg) into the perineurium of the nerves of the brachial plexus 5-10 minutes prior to transection can be efficacious in providing excellent post-operative analgesia.
- 2% lidocaine, or a combination of 2% lidocaine and 0.5% bupivicaine (0.2 mL/kg total volume) can also be used.

Paravertebral brachial plexus block (newer technique):

- The traditional brachial plexus nerve block requires large volumes of local anesthetic to get complete blockade of the plexus, and only blocks the limb distal to the elbow.
- The paravertebral brachial plexus block has been recommended as an alternative for dogs.
- The nerves the C6, C7, C8, and T1 are blocked as close as possible to the intervertebral foramina, instead of in the axillary region.
- The scapula is moved caudally to expose the large transverse process of the sixth cervical vertebra and the first rib
- Ventral branches of C6 and C7 are blocked as they cross the dorsal surface of the transverse process of C6 by inserting a needle dorsal to the process and directing it toward the cranial and then caudal margins of the process
- Ventral branches of C8 and T1 are blocked on the lateral surface of the first rib by directing the needle to the cranial and caudal border of the dorsal part of the first rib, close to the articulation with the vertebra.
- The injection volume is 1–3 mL in dogs or 0.1–0.3 mL in cats of 2% lidocaine or 0.5% bupivicaine, using a 22-gauge, 1-inch needle.
- Both types of blocks can cause blockade of the phrenic nerve, so should not be performed bilaterally.
- Pneumothorax can occur with both blocks.

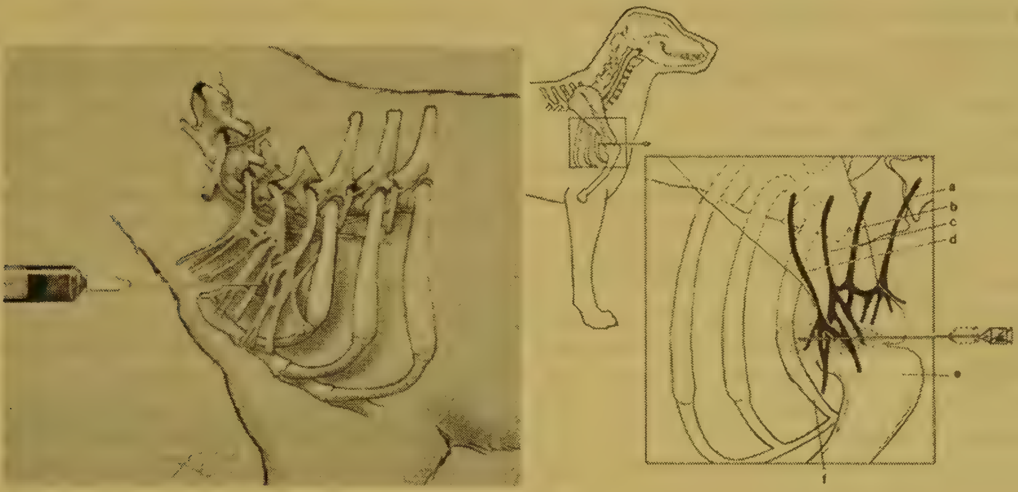

Figure 3. Brachial plexus nerve block techniques.

Onychectomy (Declaw) Nerve Blocks for Cats

- Blockade of the superficial branches of the radial nerve, the median nerve, and dorsal and palmar branches of the ulnar nerve.
- Effective analgesia for feline onychectomy or orthopedic surgery of the distal extremity.
- 0.5% bupivicaine is the drug of choice for this block due to its long duration of action.
- Inject 0.1 to 0.3 mL of 0.5% bupivicaine (not exceeding the total maximum dosage) at each of three locations:
  - Medial to the accessory carpal pad to block the median nerve and palmar branch of the ulnar nerve.
  - Lateral and proximal to the accessory carpal pad to block the dorsal branch of the ulnar nerve.
  - At the dorsal-medial aspect of the proximal carpus to block the superficial branches of the radial nerve.
  - Alternatively, a simple 'ring' block around the carpus will also block these nerves.

Intravenous Regional (BIER) Nerve Blocks

- Intravenous regional anesthesia (IVRA) is a rapid and reliable method for producing short-term (<1 hour) anesthesia of the distal extremities.
- Minimal systemic absorption of drug, resulting in decreased incidence of toxic side effects.
- The duration of analgesia once the tourniquet has been removed is minimal, and other analgesics should be provided.

Technique

- An IV catheter is placed into a distal vein of a limb (cephalic v., saphenous v.).
- A rubber tourniquet is placed around the limb proximal to the IV catheter.
- Once the tourniquet is secured, **lidocaine**, 2.5–5 mg/kg in dogs, and 2–3 mg/kg in cats, is injected into the catheter.
- Five to10 minutes are required to achieve maximum (surgical) anesthesia, which will last up to 60 minutes.

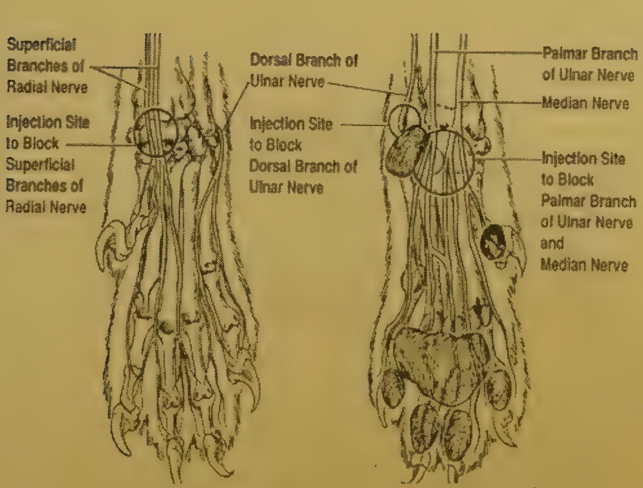
Superficial Branches of Radial Nerve
Injection Site to Block Superficial Branches of Radial Nerve
Dorsal Branch of Ulnar Nerve
Injection Site to Block Dorsal Branch of Ulnar Nerve
Palmar Branch of Ulnar Nerve
Median Nerve
Injection Site to Block Palmar Branch of Ulnar Nerve and Median Nerve

Figure 4. Onychectomy (declaw) nerve blocks for cats

Figure 5. Intravenous regional or Bier block.

- Sensation will return within 5 to 10 minutes of removing the tourniquet.
- Provides a blood-free surgical site and has been used to inject antibiotics and obtain high tissue concentrations in a distal extremity.
- Limit procedure to ≤ 60 minutes to minimize dcomplications resulting from blood flow deprivation to the limb.

Intercostal Nerve Blocks

- Effective analgesia for thoracotomy or rib fractures.
- The intercostal nerves descend in the intercostal space along the caudal border of each rib, associated with the ventral branches of the intercostal artery and vein.
- The block is performed as dorsally as possible, near the intervertebral foramen.
- The needle is advanced onto the rib, then "walked" caudally until it enters the tissues behind the caudal border of the rib.
- After the syringe is aspirated, the local anesthetic is injected.
- This procedure is repeated to block three intercostal nerves in front of the incision and three caudal to it, in addition to the site of the incision.
- Can be performed immediately after induction of anesthesia for pre-emptive analgesia.
- Articaine may be better to use pre-emptively, when the nerves cannot be visualized, due to its ability to spread through the tissues.
- This block can also be performed prior to closure of the chest wall, from the pleural side.
- Approach from the pleural surface also allows blockade of the dorsal branch of the intercostal nerve, by injecting close to the point at which the nerve exits the spinal canal.
- A total dose of 4 mg/kg of 0.5% bupivicaine (or 4% articaine) in dogs and 2 mg/kg in cats is dividing amongst all the sites.

Maxillary and Mandibular Nerve Blocks

- Excellent analgesia for maxillectomy, mandibulectomy and dental extractions.
- Blocking the maxillary nerve as it exits the infraorbital foramen (A on diagram) will provide analgesia to the canine and incisor teeth in the upper jaw (I avoid this in cats due to proximity of the orbit).
- Blocking the mandibular nerve as it exits the mental foramen (D on diagram) will provide analgesia to the lower incisors.
- To provide analgesia to the entire upper jaw, the maxillary nerve is blocked at the perpendicular portion of the palatine bone, between the maxillary foramen and the foramen rotundum (B on diagram).
    - The needle is inserted through the skin at an angle of 90°, in a medial direction, ventral to the border of the zygomatic arch and approximately 0.5 cm caudal to the lateral canthus.
    - Advance the needle in close proximity to the pterygopalatine fossa.
    - Local anesthetic is administered where the maxillary nerve courses perpendicular to the palatine bone, between the maxillary foramen and the foramen rotundum.
- The mandibular nerve, blocked at the point of entry of the nerve into the mandibular canal at the mandibular foramen, will provide analgesia to the entire lower jaw (E on diagram).
    - The needle is inserted at the lower angle of the jaw, rostral to the angular process.
    - The needle is advanced dorsally, against the medial surface of the ramus of the mandible, to the palpable lip of the mandibular foramen and local anesthetic is injected.
- A 25-gauge 5/8- to 1-inch needle is used and 0.2 mL/kg of 0.5% bupivicaine or 4% articaine is deposited at each site.

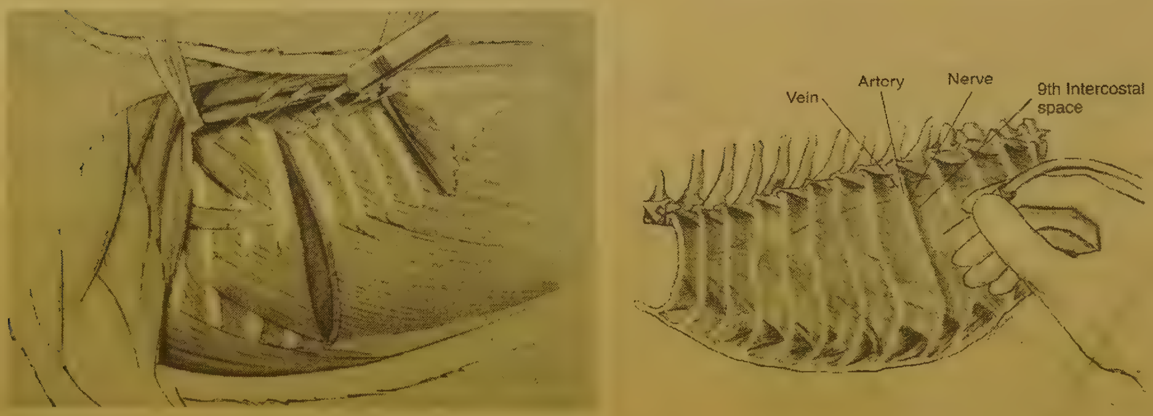

Figure 6. Intercostal nerve blocks.

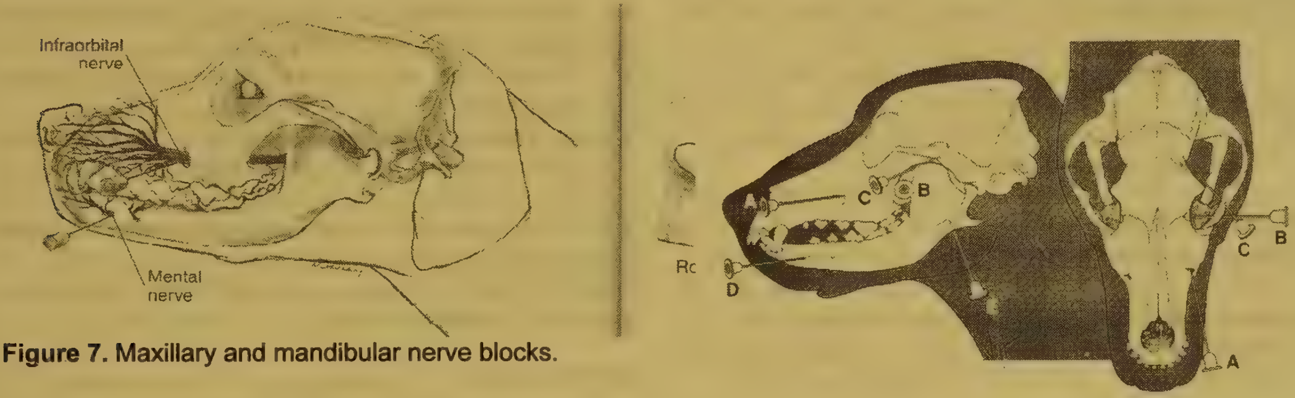

Figure 7. Maxillary and mandibular nerve blocks.

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CHALLENGING FELINE ANESTHESIA CASES

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HYPERTHYROIDISM

- Prone to dysrhythmias, tachycardia, hypotension, and decreased cardiac output, particularly if concurrent hypertrophic cardiomyopathy
- Make the patient euthyroid prior to anesthesia with methimazole

HYPERTROPHIC CARDIOMYOPATHY (HCM)

- Hypertrophy of cardiac muscle results in impaired myocardial perfusion in the face of increased myocardial oxygen requirements.
- Increased contractility can result in a muscular subaortic stenosis forming during systole, causing a dynamic outflow obstruction and mitral regurgitation.
- Sympathetic nervous system (SNS) stimulation, tachycardia, increased contractility, and increased systemic vascular resistance and afterload should be avoided, as these will reduce cardiac output, concurrently causing an increase in myocardial oxygen demand, predisposing to myocardial ischemia and dysrhythmias.
- If it is possible to delay anesthesia, HCM cats in failure should be stabilized with calcium channel blockers or beta-blockers and pulmonary edema treated.

Anesthetic Management

- Provide supplemental oxygen, if it doesn't stress the cat.
- Avoid SNS stimulation, hypoxemia, hypercarbia, excitement, fear, pain, and stress.
- Avoid hypovolemia and a decrease in venous return; correct fluid deficits prior to general anesthesia.
- If tachycardia is impairing diastolic filling, resulting in hypotension, and no obvious cause of the tachycardia can be found and treated (ie, pain), treat with a beta-blocker (propranolol).
- Avoid hypothermia, as shivering during recovery can increase metabolic oxygen demand by 300%.
- Avoid anticholinergics, but, if necessary, glycopyrrolate is preferred, as it is less likely to cause tachycardia than atropine.
- Avoid xylazine, thiobarbiturates, propofol, and halothane, as these predispose to dysrhythmias and decreased myocardial contractility.
- Avoid ketamine or tiletamine (Telazol®), as both are SNS stimulants.
- Low doses of acepromazine can be used (anti-dysrhythmic).
- Avoid high doses to minimize reduced venous return and cardiac output, and hypothermia.
- Maintain preload with the cautious administration of IV fluids (≤5 mL/kg/hour)
- Monitor CVP and renal output during prolonged anesthesia.
- For hypotension, avoid using a sympathomimetic alpha1-agonist, such as phenylephrine, rather than a beta1-agonist.
- If hypertension occurs, deepen anesthesia with sevoflurane or isoflurane.
- Administer analgesics, mild sedation, and oxygen during recovery.

Premedication

- Midazolam (0.2 mg/kg) or acepromazine (0.01–0.025 mg/kg) combined with butorphanol (0.2–0.4 mg/kg) or hydromorphone (0.05–0.1 mg/kg), IM.
- Administer the opioid first, and the benzodiazepine 10 minutes later, to avoid excitement.
- Low dose medetomidine (2–5 micrograms/kg) can reduce both tachycardia and dynamic outflow obstruction in HCM cats, and is also an anti-dysrhythmic. It may be combined with an opioid.

Induction

- Propofol (3–4 mg/kg IV) if HCM very mild
- Etomidate (1–3 mg/kg IV)
- Propofol or etomidate can be combined with diazepam (0.2 mg/kg, IV) to reduce dosages required for induction.
- Mask with isoflurane or sevoflurane

Maintenance

- Isoflurane or sevoflurane (has less of a tendency to cause tachycardia).

ANESTHESIA FOR CATS WITH ACUTE RENAL FAILURE (ARF), CHRONIC RENAL FAILURE (CRF), URETHRAL OBSTRUCTION, OR RUPTURED BLADDER

Anesthetic Effects on Renal Function

- Most general anesthetic agents decrease glomerular filtration rate (GFR) directly, by causing peripheral vasodilation and decreasing renal blood flow (RBF), or indirectly, by causing decreased stroke volume (SV), heart rate (HR), and cardiac output (CO).
- RBF auto-regulation is maintained at lighter planes of anesthesia (≤ 1 MAC), but not at the deeper levels of anesthesia required for surgery.
- Renal responses to anesthetics also depend on the patient's hydration status.
- Intraoperative renal ischemia can result in ARF post-anesthesia.
- Urine production < 0.5 mL/kg/hour during anesthesia and recovery is considered oliguria, and may be indicative of ARF, secondary to renal ischemia. Renal ischemia can be due to:

Systemic Hypotension

- Uncorrected fluid deficits and inadequate replacement of ongoing losses
- Excessive vasodilation or decreased contractility due to deep anesthesia or high doses of thiopental, propofol, or acepromazine

Renal Vasoconstriction

- Administration of epinephrine or significant (>20%) blood loss can result in severe renal vasoconstriction, increased renal vascular resistance, and up to 40% reduction in RBF.
- Aldosterone, vasopressin, renin, and catecholamines are released with stress and decrease RBF and GFR.

Treatment

- If no cardiac failure or pulmonary edema, a fluid challenge of 10–30 mL/kg of balanced, isotonic crystalloid or 5–10 mL/kg of colloid can be attempted twice.
- Measure CVP before and during fluid challenge.
    - If CVP high, fluid challenge contraindicated
    - If CVP negative, patient is hypovolemic and fluid challenge is indicated.
- If normovolemic, but still oliguric:
    - Dopamine (2–7 µg/kg/min) or dobutamine (5–8 µg/kg/min).
    - If sympathomimetics have been unsuccessful:
        - Lasix (0.5–1.0 mg/kg)
        - Mannitol 0.25–0.5 mg/kg for osmotic diuresis

IMPLICATIONS OF RENAL DISEASE AND ANESTHESIA

Azotemia and Acidosis

- Increased permeability of the blood-brain barrier and sensitivity of the CNS to anesthetics
- Increased fraction of unbound, active drug(s) in the plasma
- Correct the azotemia and acidosis prior to anesthesia with IV fluids, $NaHCO_3$ (0.5–1 mEq/L), and peritoneal or hemodialysis.
- Use lower doses and titrate to effect.

Electrolyte Disturbances

- Hypokalemia (CRF) predisposes to hypotension and dysrhythmias.
- Treat with supplementation prior to anesthesia and avoid placing potassium in anesthesia fluids to avoid rapid administration.
- Hyperkalemia (serum potassium > 6.0 mEq/L) (ARF, urinary obstruction or ruptured bladder), predisposes to:
    - Dysrrhythmias: 1st degree AV block, peaked t waves, loss of P waves, wide QRS complexes, cardiac arrest, death
    - Treat with IV fluids, NaHCO3 (0.5–1.0 mEq/dL, IV), 50% dextrose (2 mL/kg, IV), and regular insulin (0.2 IU/kg, IV; monitor blood glucose), until serum K+ concentration is < 6.0 mEq/dL
- Hypocalcemia can decrease automaticity, contractility, BP, and CO.

Hypoalbuminemia

- Reduction of dosages required of highly protein bound drugs (benzodiazepines, thiopental, or propofol).
- Reduction of the plasma oncotic pressure, resulting in greater chance for pulmonary edema to develop with fluid therapy.

Anemia

- Reduced oxygen carrying capacity, predisposing to hypoxia
- The cardiovascular system may become hyperdynamic in an attempt to maintain oxygen delivery, resulting in hypertension, tachycardia, and increased CO, resulting in decreased cardiac reserve.
- Transfuse prior to surgery if PCV $\leq$ 20%.

CRF or ARF and Anesthesia

- May present polyuric, polydypsic, dehydrated, uremic, acidotic, hypokalemic (CRF), hyperkalemic (ARF), hypoproteinemic, and/or anemic.
- CRF patients may present with hypertension, and may be either hypertensive or severely hypotensive during anesthesia.
- Hypertensive patients should be treated with a calcium channel blocker or ACE inhibitor prior to anesthesia; this may make them more prone to develop hypotension under anesthesia, so provide supplemental fluids and monitor BP.
- .A MAP of > 80 mmHg should be maintained in chronically hypertensive patients during anesthesia to maintain renal perfusion.
- Ketamine, morphine, hydromorphone, and diazepam have active metabolites that are excreted by the kidneys, and should be used cautiously.
- NSAIDS are contraindicated.

Urethral Obstruction or Ruptured Bladder and Anesthesia

- Present with hypovolemia, hyperkalemia, azotemia, acidosis (metabolic and respiratory), hyperphosphatemia, hyperglycemia, hypocalcemia, and hyponatremia.
- The ECG should always be evaluated prior to and during anesthesia:
- ECG changes due to hyperkalemia include small or absent P waves, peaked T waves, prolonged P-R interval, increased duration of QRS, shortened Q-T interval, bradycardia, and sinus arrest; some cats seem to become tachycardic.
- Premature ventricular complexes (PVCs) may also be seen in these patients, particularly if acidotic or hypoxemic.

- If K+ > 7.0 mEq/l, treat until ≤ 6.0 mEq/L prior to anesthesia
- Expect intraoperative changes in serum K^+ with fluid shifts occurring during anesthesia.
- A grossly distended bladder can prevent adequate ventilation, and positive pressure ventilation (PPV) may be required during anesthesia.
- Avoid the rapid drainage of large volumes of peritoneal fluid and urine:
  - Removal of this hydrostatic pressure from the abdomen can allow rapid vasodilation of abdominal vessels and rapid loss of fluid from the inflamed peritoneum resulting in severe hypotension.
  - Sudden loss of severe visceral nociceptive input from a distended bladder may cause a marked decrease in plasma catecholamines, and contribute to cardiovascular collapse.

Anesthetic Management of Patients with Renal Disease

- Always carefully titrate doses to effect.
- Avoid further insult to kidneys due to hypotension, hypovolemia, or production of nephrotoxic metabolites.
- Correct uremia, fluid deficits, and electrolyte and acid-base abnormalities prior to anesthesia
- Pre-anesthesia diuresis for 3 to 4 hours (1.5–3 x maintenance rate) can help prevent intra-operative hypotension, even in normovolemic cats (if cardiac function is normal).
- Intraoperative IV fluid therapy (10 mL/kg/hour).
  - Choice of fluid depends on underlying electrolyte abnormalities, 0.9% saline, Normasol R, or LRS is usually adequate.
  - If hypoproteinemic (< 2 g/dL), administer colloid (Hetastarch or Dextran 70; 5–10 mL/kg) and/or plasma.
- Monitor CVP during anesthesia to help assess blood volume, particularly if there is concurrent cardiac disease.
  - If CVP > 10 cmH_20, decrease or discontinue fluids and administer sympathomimetics and/or diuretics.
- Monitor urine production intraoperatively and postoperatively, if possible, by placement of a urinary catheter.
- Monitor blood pressure during anesthesia, keeping the MAP >60 mmHg, but > 80 mmHg in chronically hypertensive patients.
- Providing adequate analgesia will allow MAC reduction and lower concentrations of isoflurane or sevoflurane.
- Use sympathomimetics to support BP and maintain RBF:
  - Dobutamine: 5–10 μg/kg/min IV
  - Dopamine:
    - 5–10 μg/kg/min IV: Improves CO and RBF
    - > 10 μg/kg/min increases renal vasoconstriction, and decreases RBF
  - Ephedrine: 0.06 mg/kg IV (effects last 20–60 minutes)
- Administer oxygen during recovery, particularly if the patient is anemic and/or hypothermic.
- Administer perioperative analgesia to avoid SNS stimulation and reduced RBF.
- Expect marked diuresis post-surgery and monitor electrolyte and acid-base status closely.

Premedication

- Buprenorphine (0.01 mg/kg) or butorphanol (0.2–0.4 mg/kg) have minimal effects on renal function.
- Morphine has an antidiuretic effect and mu agonist opiates can cause urinary retention, making monitoring of urine output to assess renal function inaccurate.
- Midazolam or diazepam (0.2 mg/kg) has minimal effects on renal function.

Induction

- Propofol (2–4 mg/kg) if normovolemic
- Mask or tank with volatile anesthetic
- Etomidate (1–3 mg/kg, IV)
- Ketamine (5 mg/kg) and diazepam (0.25–0.5 mg/kg) IV, if renal disease is mild to moderate, or if release of the urinary obstruction and subsequent diuresis is probable.

Maintenance

- Isoflurane or sevoflurane

ANESTHESIA FOR HEPATIC LIPIDOSIS OR BILIARY OBSTRUCTION

Feline Hepatic Lipidosis

- Present with dehydration, electrolyte and acid-base abnormalities, coagulopathies, and hypo-albumenemia.
- Severe hepatic lipidosis may result in encephalopathy, requiring lower doses of anesthetic drugs.
- Prolonged recovery has been associated with oxymorphone, hydromorphone, butorphanol, propofol, diazepam, etomidate, and ketamine, so use cautiously.

Biliary Obstruction

- Present with hypovolemia, electrolyte and acid base abnormalities, coagulation abnormalities, hypo-albumenemia, hypoglycemia, and GI ileus (predisposing to regurgitation and aspiration).
- Expect significant postoperative diuresis; careful calculation and replacement of ongoing losses (urine output; serial weights) will maintain renal perfusion.
- Two of the most serious perianesthetic complications in these patients are hypotension and acute renal failure.

Pathophysiology

- Bile duct obstruction induces profound diuresis, as bile salts and products of hepatic metabolism are excreted by the kidney.
- Cardiovascular function is depressed directly by bile salts and other toxins, and responsiveness to angiotensin II and norepinephnine is blunted.
- The combination of hypovolemia and impaired cardiovascular function leads to systemic hypotension and renal ischemia.
- Jaundiced patients, with or without bacterial infection, have elevated concentrations of endotoxin in their blood.
- Endotoxin can cause low-grade intravascular coagulation, renal vasoconstriction, and renal failure.
- Patients with bile peritonitis may be severely hypovolemic, presenting with clinical signs of shock.
- These patients are also very painful, and may require buprenorphine to control pain.

Anesthetic Protocols

- May have decreased hepatic enzyme function, so use drugs that don't rely heavily on hepatic metabolism or that can be reversed
- Avoid morphine as it causes constriction of the sphincter of Oddi, increasing pressure in the common bile duct, potentially causing rupture.
- Benzodiazepines, buprenorphine, and butorphanol are safe and reversible with flumazenil and naloxone.
- Avoid acepromazine because of the potential to cause hypotension and reduced RBF and requirement for hepatic metabolism
- Propofol, if hypovolemia corrected (extra-hepatic sites for metabolism)
- Isoflurane, sevoflurane (minimal hepatic metabolism)

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TRANSDERMAL FENTANYL PATCHES AND ALTERNATIVES FOR LONG-TERM ANALGESIA

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Long-term pain management remains a challenge for veterinarians. In addition to economic concerns, owner compliance, off-label use, and efficacy are important in deciding which drugs to use.

OPIOIDS

Transdermal Fentanyl Patches (Duragesic®)

- Produce analgesic plasma concentrations within 12 to 24 hours and 6 to 8 hours of patch placement, in dogs and cats, respectively.
- There is **considerable individual variation in drug levels achieved over time**, making it difficult to predict the adequacy of analgesia.
- Variability can be due to differences in drug delivery and absorption rates, due to alterations in skin temperature, skin blood flow, failure of the patches to stay in place, activity levels of the animals, and individual variability in drug clearance.

Problems with the Transdermal Drug Administration Patch

- Expensive, although generic patches are now available and cost around 40% less
- Often maintain inadequate contact with the skin, resulting in reduced or no uptake of drug
- Fentanyl is a respiratory depressant and can result in hypoxemia and hypercarbia.
- Dysphoria, excessive sedation, ileus, hypothermia, constipation, and decreased appetite can occur.
- If the animal ingests the patch, respiratory depression, excessive sedation, bradycardia and death could occur.
- The potential for accidental exposure of children in the household could be fatal, and because the use of these patches is extra-label, veterinarians are potentially exposed to full liability.
- Fentanyl is a highly addictive opiate and diversion by humans for illicit use results in a significant public health risk.

Buprenorphine (Buprenex®)

- Partial mu agonist with slow onset (20–30 minutes IV, and 30–60 minutes IM), but long duration (6–8 hours).
- Efficacious for mild to moderate pain, particularly if combined with an NSAID.
- Dosage: 0.005—0.02 mg/kg, IM, IV, SQ, orally. 0.005–0.01 mg/kg epidurally.
- Given orally to cats, has 100% bioavailability due to absorption across mucous membranes.

Oral Sustained-Release Morphine

- Absorption is prolonged (6 hours) and bioavailability is low (20%).
- Efficacious in the management of chronic pain in some animals, likely due to the higher levels maintained within the cerebrospinal fluid (CSF)
- The response can be inconsistent, with cats seeming to do better with it than dogs.
- In dogs, the oral sustained release form of morphine is erratically absorbed which may explain the inconsistent responses.
- Dosage: 1.5–3 mg/kg, PO q12h in dogs, and q12–24h in cats

Codeine (Oral)

- Codeine analgesic effects result from metabolism to morphine.
- Its antitussive effects are probably due to direct action on codeine receptors.
- It can be an effective analgesic for mild pain, or as a supplement to a nonsteroidal anti-inflammatory drug (NSAID).
- Oral codeine can be given to cats, but codeine with acetaminophen is **contraindicated.**
- **Dosage:**
  - For mild to moderate acute pain in dogs 0.5–2 mg/kg PO q6–12h
  - In combination with acetaminophen: Using a 60-mg codeine and 300- mg acetaminophen fixed-dose tablet (eg, Tylenol® #4), give 1–2 mg/kg (of the codeine) PO q6–8h.
  - Using codeine alone: 1–4 mg/kg PO q1–6 hours
  - For mild to moderate acute pain in cats: 0.5–2 mg/kg PO q6–12h.

TRAMADOL

- Provides analgesia mainly via by increasing release and decreasing re-uptake of serotonin and norepinephrine in the spinal cord
- Although it is considered a non-opiate, the (+)enantiomer is a weak mu agonist, as is its (+)enantiomer metabolite.
- The (–)enantiomer acts on alpha-2 receptors and serotonin receptors.
- Wide margin of safety in humans, with minimal respiratory, cardiovascular, or GI side effects
- Low abuse potential, is not controlled by the DEA, and lacks pharmacodynamic tolerance

Veterinary Use

- Adverse effects, such as bradycardia, respiratory depression or constipation appear to be less than those seen with common pure mu agonists, such as morphine or hydromorphone.
- Dosage: 1–4 mg/kg, q6h to q8h (dogs and cats seem to vary widely in their response to this drug, so I start at a low dose and work up)
- Duration is around 6–8 hours, but some animals seem to do well on BID treatment.

- Tramadol comes as 50-mg tablets, but can be compounded in a slurry or syrup.
- Comes compounded with codeine for humans, but veterinary experience is limited

NON-STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDs)

- NSAIDs can be very effective for both acute and chronic pain management.
- Relatively safe for chronic use in dogs, but may not be suitable for chronic use in cats

Advantages to NSAIDs

- Long duration of action
- Anti-inflammatory
- No behavior modifying effects
- No cardiopulmonary depression
- Oral formulations are available
- Not controlled by the DEA.

Toxicity and Side Effects

All NSAIDs have the potential to cause:

- Clotting abnormalities
- GIT toxicity
- Nephrotoxicity
- Cats often have an increased susceptibility to the toxic effects of NSAIDs and these drugs should be used with caution in this species.
- Only ketoprofen and meloxicam are approved for use in cats.

Contraindications

- Renal, liver disease, or GI irritation
- Dehydration, hypovolemia, or hypotension
- Coagulopathies
- If receiving other NSAIDs or corticosteroids
- Pregnant, lactating or breeding animals

KETAMINE

- A noncompetitive antagonist of the N-methyl-D-aspartate (NMDA) receptor, which is associated with the phenomenon of "wind-up" or central hypersensitization of the CNS
- May also act on opioid, serotonin, and norepinephrine receptors to mediate analgesia
- NMDA receptor antagonists have analgesic, anti-allodynic, and anti-hyperalgesic properties.
- It is useful in conditions of neuropathic pain, such as diabetic neuropathy, post-herpetic neuralgia, and interstitial cystitis in people.
- Ketamine, administered as a continuous rate infusion (0.05–0.2 mg/kg loading dose, followed by infusion at 0.5–1 mg/kg/hour), provides very effective analgesia.
- At this dose, the anesthetic effects or CNS excitement effects of ketamine are not usually seen.

TRICYCLIC ANTIDEPRESSANTS (TCAs)

- Useful in the treatment of neuropathic and chronic pain
- Analgesia mediated by inhibition of norepinephrine and serotonin re-uptake in the spinal cord
- Side effects can include sedation, tachycardia, dry mouth, urinary retention, and blurred vision
- Amitriptyline:
    - 1–2 mg/kg PO q12-24h in dogs
    - 2.5–12.5 mg/cat PO once daily
- Clomipramine: 2–4 mg/kg divided BID every 24 hours

GABAPENTIN

- Anticonvulsant that is useful in the treatment of chronic neuropathic pain, and as an adjuvant for acute postoperative pain.
- Premedication with gabapentin has been shown to reduce postoperative analgesic requirements.
- Sensitization of dorsal horn neurons is induced by tissue injury and results in chronic neuropathic pain; gabapentin seems to reduce the hyperexcitability of these neurons.
- Useful adjunct to opioid or NSAID analgesia
- The main side effect is somnolence, and it is excreted unchanged in the urine, so use with caution in patients with renal disease.
- Dosage: 5–25 mg/kg PO q8h

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THE PREOPERATIVE PHYSICAL EXAMINATION AND INTERPRETATION OF PREOPERATIVE BLOOD WORK

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Prior to any anesthetic procedure, the patient's health should be evaluated. This includes conducting a physical examination (PE) prior to induction, completing pre-anesthetic blood work, which should include a complete blood count (CBC) with differential and an internal organ function screen. The CBC with differential and internal organ function screen should be performed within 48 hours prior to anesthetic induction. In addition, the patient's medical record should be thoroughly reviewed, and an IV catheter should be placed. All physical examination findings should be recorded in the medical record, and blood test results reviewed and also recorded. Based on these comprehensive findings, the best anesthesia protocol can then be selected.

CANINE/FELINE PREOPERATIVE PHYSICAL EXAMINATION

The goal of the preoperative physical examination is to determine the patient's health status prior to induction. The conditions to review and evaluate include history and drug therapy, bleeding disorders, hyperthermia, anesthesia problems, shunts, myopathies, and pre-existing organ compromise. One of the two most common times for adverse anesthesia events to occur is during induction. The second is during recovery. Ensuring that the patient receives a thorough physical examination prior to induction will help minimize adverse anesthesia events. If illness is detected upon the physical exam, different best practices (protocols) can be followed that best suit the pet's individual needs. The physical examination can be divided into five categories:

- Assessing capillary refill time and pulse quality,
- Evaluating the mucous membranes for adequate perfusion,
- Auscultating the heart to assess for cardiac health,
- Auscultating the lungs to assess respiratory condition and
- Evaluating the temperature to plan for hypothermia or hyperthermia.

At the beginning of the visit, ensure that an adequate weight has been recorded. During this time, it is beneficial to assess the pet's temperament and disposition. If the patient is a fractious pet, the goal is to immobilize, obtain the necessary blood sample, place the IV catheter and perform the physical examination/patient evaluation immediately. The immobilizing agent should serve as a premed or induction agent.

Capillary Refill Time

A capillary refill time of less than 2 seconds is normal. If the pet has a normal capillary refill time, proceed with the rest of the PE. Anything longer than two seconds is abnormal and subsequently the pet should be evaluated for shock. If the pulse quality is normal, proceed with the rest of the PE. The next part of the PE involves evaluating the femoral pulse rate/heart rate ratio. Any ratio greater than 0.95 is considered normal and the PE can be continued. Ratios less than 0.95 are abnormal and a cardiac protocol should be initiated. Finally, evaluate the pulse quality. In a normal pet, this should be firm and steady. If it is abnormal, again, a cardiac best practice (protocol) should be initiated. Below is a table listing abnormal heart rate values in the awake pet.

Abnormal Heart Rate Values (Awake Pet)		
Species	Greater than	Less than
Small Dog	140	100
Medium Dog	140	80
Large Dog	100	60
Cat	160	120

If the heart rate falls in either the "greater than" or "less than" categories, it is important to follow the cardiac best practice (protocol).

Mucous Membrane Color

Normal mucous membranes are a pink color. If they are pale or have a hemorrhagic appearance, evaluate the hematocrit (HCT) and hemoglobin concentration. If these are normal, proceed with the PE.

Auscultate the Heart

If the heart sounds normal, proceed with the PE. If there is a cardiac murmur, consider the age of the pet. If the pet is young, consider a congenital heart problem or physiologic murmur. Perform an exercise tolerance test. If the murmur is physiologic, the murmur should resolve. If not, consider a cardiac best practice (protocol). If the murmur is an ejection/systolic murmur, consider stenosis and refer to a cardiologist, unless it is an emergency. If a murmur is heard in a mature pet, suspect acquired cardiac disease and proceed to a cardiac best practice.

Auscultate the Lungs

If normal air movement is heard, proceed with the PE. Abnormal sounds may include no movement, noncompliance and/or dry/moist rales. If these sounds are heard, postpone anesthesia if possible and make a clinical diagnosis. Be sure to review the pulmonary protocol before continuing with anesthesia. Also, consider the pet's weight. If the pet is obese, follow a pulmonary best practice (protocol).

Temperature

In cases of hypothermia (body temperature is less than 99°F), give warm 2.5% dextrose in 0.45% sodium chloride IV and warm the pet. If there is no improvement, postpone anesthesia and look for other causes of hypothermia. If the pet has hyperthermia (body temperature of greater than 103°F) check the white blood cell count. If it is elevated, postpone anesthesia if possible. Otherwise, administer 0.9% sodium chloride IV, and IV cefazolin only.

BLOOD WORK EVALUATION

Within 48 hours prior to induction, it is important to review the patient's CBC with differential and internal organ function screen.

Hematocrit, Hemoglobin, and RBC count

Either postpone anesthesia or administer a blood transfusion if the patient has a hematocrit (HCT) of less than 25% and/or a hemoglobin concentration of less than 10. If the HCT is greater than 40% in the cat, and greater than 45% in the dog, review a pre-renal azotemia best practice. If other abnormalities exist, use the appropriate protocol.

Platelets, Clotting Problems

Postpone or transfuse a pet prior to surgery if his/her platelet count is less than 125,000, is von Willebrand's positive, or has some other clotting disorder. Confirm the platelet abnormality/clotting problem by reviewing a fresh blood smear, checking the buccal mucosal bleeding time (BMBT) and evaluating the activated coagulation time (ACT).

WBC Count

If the WBC count is less than 4000, or greater than 15,000, review a blood smear. If neutrophilia with a left shift exists, postpone surgery and make a clinical diagnosis. Otherwise, use an abdominal best practice.

Mean Corpuscular Volume (MCV), Mean Corpuscular Hemoglobin (MCH), and Mean Corpuscular Hemoglobin Concentration (MCHC)

These values will vary depending on the age of the pet. If these values are abnormal, check the pet with pulse oximetry. If oxygenation is low, check liver function. If the MCV is low, consider checking bile acids. Postpone surgery if possible and select a liver protocol to follow.

INTERNAL ORGAN FUNCTION SCREEN

BUN/Creatinine

If the BUN/creatinine is low, review the liver protocol. If it is high, palpate the bladder to check for obstruction. If there is an obstruction, perform a urinalysis (UA) by cystocentesis and follow a post renal protocol. If the urine specific gravity (USG) is high, rehydrate the pet. A high USG for a dog is greater than 1.020, while greater than 1.030 is high for a cat. Address the underlying cause prior to proceeding and consider following a pre-renal azotemia protocol. If the BUN is elevated, but the creatinine is normal, consider gastrointestinal (GI) bleeding. If the USG is low (>1.020 for a dog, >1.030 cat) check other UA parameters. Consider renal disease as a differential diagnosis, and follow a renal best practice.

Calcium

If calcium is elevated, look for renal disease or neoplasia (lymphoma, perianal). If calcium is low, check albumin levels and consider Addison's. In addition, performing an electrocardiogram may be beneficial. If this is normal, proceed.

ALT/Bilirubin/ALKPhos

If these are high, evaluate for liver disease. If the total bilirubin is less than 2.0, check bile acids and evaluate electrolytes. In addition, consider obtaining radiographs and ultrasound. If the electrolytes are abnormal, treat this as a cardiac case. If liver disease is present, avoid using acepromazine and follow a liver best practice.

Albumin/Total Protein

If the total protein is less than 3.5, look for possible causes. Give plasma if possible. Administer diphenhydramine 1.0 mg/lb, with a maximum dose of 50 mg, IM prior to infusion. Wait 30 minutes for effect. Remove acepromazine from the premeds and continue as normal.

Potassium

If potassium levels are high or low, verify the sample value. Look for a potential cause such as urethral blockage, ruptured bladder or compromised renal function. Consider performing an ECG.

Glucose

If glucose levels are less than 100, look for a potential cause. Start 2.5% dextrose in 0.45% sodium chloride IV. If glucose levels are above 200, do a serum fructosamine (SF) test and postpone anesthesia. If SF test positive, follow a diabetic best practice or postpone anesthesia and stabilize the pet.

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MANAGEMENT OF THE ANESTHETIC EMERGENCY

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Emergencies are surgical cases that require anesthesia within 15 minutes to save the patient's life, and though "infrequent patient deaths" might have been considered successful in the past, they can no longer be labeled as quality anesthesia. Our goal should be for the patient's condition to be equal or better than the pet's condition prior to anesthesia. Non-fatal adverse events must be looked at as critically important when determining quality anesthesia, especially when they result in an emergency. Poor perfusion doesn't always result in the patient's death. For example, we want to avoid behavior changes or cortical blindness as a result of a hypoxic event that damages brain tissue during anesthesia.

Outcome analysis over the past years has noted many things:

- Anesthetic reactions are truly very rare.
- Lack of proper monitoring results in the appearance that patients are alive one minute and dead the next.
- Lack of understanding regarding proper drug usage and effects is common.
- Development of unique protocols (ie, bypassing standards) increases morbidity rates and mortality rates.

It is important to not view anesthesia solely as selecting the right drug, but to look at how the pharmacology of the anesthetic agents affects patient perfusion while maintaining a "state of consciousness" that allows a procedure to be performed. If an experienced doctor has the correct drug but the monitoring equipment is not functioning, an adverse anesthesia event or a fatal outcome can still result. Perfusion must be maintained during anesthesia, and as such, patients that are not monitored have higher morbidity and mortality rates.

One of the many things we've learned from outcome analysis is that all drugs are not compatible. Their physiological effects need to be understood well enough to be certain of compatibility. This complex matrix of premeds, induction agents, maintenance agents, and emergency drugs makes well thought out protocols and standards essential.

ANESTHESIA INDUCTION

In general, monitoring patients carefully during the induction phase prevents adverse events. Monitor multiple systems for trends. Continual monitoring and observation should be recorded in the medical record every five to ten minutes until recovery. The primary cause for crisis during or after anesthesia is the failure to notice a problem when it occurs.

If the patient is in shock, anesthesia is contraindicated. If possible, correct shock prior to induction. When correcting shock is not possible (during an emergency), mask induction with sevoflorane may be indicated. Avoid stress when utilizing mask induction; if heart rate increases by 25% or more, allow patient to relax, then administer the appropriate intravenous (IV) induction agent.

EMERGENCIES

Again, emergencies are surgical cases that require anesthesia within 15 minutes to save the patient's life. In event of an emergency when correcting shock is not possible, mask induction with Sevoflorane may be indicated. Avoid stress when utilizing mask induction; if heart rate increases by 25% or more during mask induction, allow patient to relax, and administer appropriate IV induction agent.

True emergencies requiring immediate anesthesia are rare. With true emergency anesthesia, premeds, including butorphanol, may not have had time to take complete effect. Use the minimum amount of drugs for induction and the lowest sevoflorane percent possible for the situation.

Most pets will have a better outcome if stabilized before anesthesia or surgery. A true emergency requiring immediate surgery would include an airway obstruction or acute life-threatening hemorrhage. Gastric dilatation-volvulus (GDV) cases require stabilization and decompression prior to general anesthesia. They don't meet the definition of "emergency" as used in this protocol.

Indicators of an Emergency

Many indicators of an emergency can be noticed if the patient is being monitored on a regular basis. Indicators may include the following:

- Poor or diminishing pulse quality
- Decreased oxygenation (cyanosis may not be present)
- Bradycardia
- VPC

If monitoring End Tidal CO_2 (ET CO_2), patients should be maintained between 35–50 mm Hg. Causes of changes in the exhaled concentrations of carbon dioxide (ET CO_2):

- Increase (>50 ET CO_2) caused by:
    - Hypoventilation
    - Endotracheal tube that is too small (ie, narrowed airway)
    - Malignant hyperthermia
    - Sepsis
    - Rebreathing (CO_2 is not being removed by soda lime)
    - Administration of bicarbonate
    - Insufflation of carbon dioxide during laparoscopy
- Decrease (<35 ET CO_2) caused by:
    - Hyperventilation

- Hypothermia
- Low cardiac output
- Pulmonary embolism
- Accidental disconnection from the anesthetic machine or ET tube extubation
- Cardiac arrest If patient has an ET CO_2 <35 mm Hg, the frequency of ventilation should be decreased. If patient has an ET CO_2 >50 mm Hg, the frequency of ventilation should be increased.

Fluid Therapy

Avoid using fluids containing dextrose in critical cases (cardiac, pulmonary, abdominal), as hyperglycemia is related to an increased risk of re-perfusion injury in the event of cardiac arrest. The 0.9% sodium chloride fluid is also preferred in these cases, as it does not contain additives that will interact with emergency drugs.

Emergency Protocols

1. If a patient's pulse quality or oxygen saturation diminishes, increase delivery of oxygen and fluids. If this fails to improve the patient's condition, give Neo-synephrine, an alpha-1 agonist, intranasally. Since this is a pure alpha-1 adrenergic agent, it causes vasoconstriction to the arterioles without affecting cardiac output.
2. If Neo-synephrine does not result in improved pulse quality and oxygen saturation, administer ephedrine through an IV. Ephedrine indirectly stimulates both alpha-1 and beta-1 agonist activity (causing vasoconstriction and increased cardiac output) by causing the release of norepinephrine. Norepinephrine also affects beta-2 adrenergic receptors, but to a much lesser degree.
3. Give dobutamine, a pure beta-1 agonist, through an IV as a slow drip to increase cardiac output, if the previous steps fail to improve pulse quality and oxygen saturation.
4. As a last step, give epinephrine via IV (it is an agonist to alpha-1s, beta-1s, and beta-2s).

CPR Protocol

Cardiopulmonary arrest (CPA) can be the natural ending of a full life or can result due to trauma or disease states. If CPA is due to a potentially reversible traumatic or medical condition, then prompt application of sound cardiopulmonary resuscitation (CPR) techniques while addressing the underlying cause of the arrest may allow restoration of life signs.

Effective CPR requires a highly trained, efficient and coordinated team, appropriate monitoring devices and medications, and prompt application of CPR techniques. Even with aggressive and effective CPR, survival rates remain low (less than 10%). Controversy exists as to the best CPR techniques and protocol. Therefore, we have combined recommendations from many sources to produce a reasonable CPR process that will benefit the greatest number of patients and utilizes equipment, techniques and medications that should be available in all of our hospitals.

The goal of the following CPR protocol is to provide an outline for closed chest CPR in dogs and cats. This protocol is a template, and to be effective will require training of a team of doctors and nurses that can work together efficiently. The CPR protocol only applies to anesthetic cases once cardiopulmonary arrest is noted.

Recommended team training should include:

- Familiarizing all doctors and paraprofessionals with the protocol.
- Developing a hierarchy of who would be "running the code" (the doctor will usually be running the code but a lead nurse may need to initiate the code). Conduct frequent drills with your team (consider bringing in a stuffed animal as the dummy). This should include the leader assigning duties and directing the code.
- Rotating teams and individual responsibilities during the code drill so that each team member is comfortable doing each job during a code.
- Determine division of labor during a code by the number of team members available. A person may have more than one job responsibility. Assigned roles of responsibility include:
    - Running the code
    - Ventilation
    - Chest compressions (need to rotate the person doing compressions every 3 to 4 minutes to keep up adequate strength of compressions)
    - IV catheter placement, fluid and medication administration
    - Gopher
    - Monitoring
    - Recording

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EVIDENCE-BASED BEST PRACTICES PET ANESTHESIA FOR HEALTHY, FRACTIOUS, AND ILL PATIENTS

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Anesthesia in the pet practice has always been one of the more challenging and complex procedures that a practitioner performs, and yet, it is done every day with hardly a second thought. Even more challenging is the wide variation of anesthesia practices used by different doctors. There is a need to standardize anesthesia protocols for use by general practitioners.

Banfield's anesthesia standards and best practices (protocols) are a result of this thinking. Banfield has the luxury of evaluating more than 125,000 general anesthetic cases a year. By utilizing practice standards and protocols, standardized equipment and ongoing outcome analysis (part of the peer review process—a concept taken from human medicine), a constant process of improvement through learning from ongoing experience occurs.

STANDARDS AND BEST PRACTICES

Anesthesia is often considered to be synonymous with the anesthetic medications used. While the choice of anesthetic agents is important to case outcome, it is only a small portion of complete and successful anesthesia. It is important not to view anesthesia solely as selecting the right drug, but to look at how the pharmacology of the anesthetic agent affects patient perfusion while maintaining a "state of consciousness" that allows a procedure to be performed. To accomplish perfusion-maintenance, other factors besides pharmacology need to be considered. A total system for anesthesia is necessary which results in the development of standards and protocols.

When broadening the discussion of what is included in excellent anesthesia, equipment, patient health status and evaluation (including blood work), drugs and monitoring must all be considered. If an experienced doctor has the correct drug but the monitoring equipment is not functioning, an adverse anesthesia event or a fatal outcome can still result. Perfusion must be maintained during anesthesia, and as such, patients that are not monitored have higher morbidity and mortality rates.

Second, drug selection must be based on a working knowledge of drug interactions and their effects on perfusion. For example, if a patient is sedated with acepromazine, will that affect the safety margin of an alpha-2 agonist? Or, if ketamine is used for an aggressive cat, should atropine be given to prevent bradycardia? One of the many things that has been learned from outcome analysis is that all drugs are not compatible. Their physiological effects need to be understood well enough to be certain of compatibility. This complex matrix of premeds, induction agents, maintenance agents, and emergency drugs makes well thought out protocols and standards essential.

HEALTHY PET BEST PRACTICE

- Perform a complete physical examination and pre-anesthetic blood work prior to any pre-anesthetic or anesthetic drug administration (fractious patients are the exception).
- Pre-anesthesia blood work includes a CBC with differential and internal organ function screen. Perform these tests within 48 hours of anesthetic induction.
- The maximum dose of acepromazine is 1.5 mg.
- The maximum dose of butorphanol is 5 mg. Additional amounts of butorphanol at a pre-anesthetic dose may be given every 1 to 2 hours as needed for post-surgical pain control.
- Premedications administered SQ or IM may need to be diluted before administration to improve drug uptake. Minimum total volume administered should be 0.5 to 3 mL depending on patient size. Dilute with sterile water to final desired volume.
- Acepromazine should be prediluted to 1 mg/mL in a separate vial to allow proper dose administration.
- Allow 30 minutes for premeds to take effect prior to induction of general anesthesia.
- Assess cardiovascular parameters after premeds have taken effect and prior to induction.
- If premeds are given more than three hours before induction, repeat premeds at ½ dose, 30 minutes before induction.
- Administer propofol slowly to effect to minimize adverse cardiovascular effects (average dose is 1 to 2 mg/lb for dogs and 2 to 3 mg/lb for cats). Bradycardia may develop after rapid administration.
- Due to propofol's rapid induction and rapid elimination (approximately three to five minutes) the "overpressure" technique is required for a smooth transition to sevoflurane. Set delivery concentrations at 3%, using an oxygen flow rate of 3 L/minute for the first 3 minutes (3%/3 L/3 min.). For this technique to be effective, the respiratory rate must be near normal or assisted ventilation is used to assure adequate intake and uptake of the inhalation agent. Following the initial three minutes, the oxygen flow is decreased to 1–1.5 L/min., and sevoflurane concentration is adjusted to effect.
- If running sevoflurane at 4% or above, look for system leaks, improper intubation, or inadequate oxygen flow rate.
- Antibiotics other than cefazolin must be administered a minimum of one hour before anesthesia or following complete recovery.

FRACTIOUS PETS

Fractious pets are defined as:

- Needing more than one pet nurse to restrain
- Requiring more than one attempt at a blood draw or jugular stick because of patient movement
- Showing any signs of aggression

Acepromazine in Fractious Pets and Epinephrine Reversal

- Epinephrine (a natural catecholamine) stimulates both alpha and beta receptors. The body can release epinephrine during a stressful event, or in an emergency.
- If an alpha-1 antagonist, such as acepromazine, is administered or on-board (ie, pre-meds), it blocks vasoconstriction of the arterioles by epinephrine through its effect on alpha-1 receptors (a dose-dependent effect).
- Epinephrine can still stimulate beta-receptors, resulting in increased heart rate and contractility (via beta-1), and vasodilatation of the vascular bed in the skeletal muscle (via beta-2). This results in pooling of blood in the vascular beds and inhibits return of blood to the heart, resulting in acute hypovolemic shock. It is therefore important to avoid using acepromazine in the fractious pet protocol.
- If epinephrine reversal is thought to have occurred, give shock doses of fluids to attempt to volume load the patient.

Protocol

- Using Telazol IM early in the course of events helps prevent catecholamine release and thus the adverse physiological events associated with catecholamines.
- Volume-dilute Telazol with sterile water to a volume of 0.5–1 mL for improved absorption.
- The maximum dose of telazol is 100 mg per dose; if after 15–20 minutes effects of medication are not adequate for restraint, the telazol dose can be repeated up to a total dose of 2 mg/lb. Most pets, depending on temperament, will be catatonic in 2 to 3 minutes. This drug will provide 8 to 30 minutes of restraint time. Telazol will lower propofol induction dose by approximately 50%.
- Avoid giving premeds; once Telazol has taken effect, give butorphanol 0.1–0.2 mg/lb SQ/IM.
- The maximum dose of butorphanol is 5 mg; follow up with additional 5 mg every 1 to 2 hours as needed
- Dilute premedications administered SQ or IM to a total volume of 0.5–3 mL depending on the patient's size. Dilute with sterile water. Volume dilution improves drug uptake.
- Antibiotics other than cefazolin must be administered a minimum of one hour prior to anesthesia or following complete recovery.
- Allow 30 minutes for premeds to take effect prior to induction of general anesthesia.
- Assess cardiovascular parameters after premeds have taken effect and prior to induction. ECG is very helpful.
- Assess depth of immobilization; some patients can be intubated without further induction agents.
- Administer propofol slowly to effect to minimize adverse cardiovascular effects. Bradycardia may develop—especially after rapid administration.
- With Telazol, "overpressure" may not be necessary—assess depth of anesthesia prior to utilizing this technique. (Due to propofol's rapid induction and rapid elimination (about a 3- to 5-minute window of duration) the technique of "overpressure" is required to assure a smooth transition to sevoflurane. Set sevoflurane delivery concentrations at three percent using an oxygen flow rate of 3 L/min (3%/3 L/3 min). To be effective, the respiratory rate must be near normal, or use assisted ventilation to assure adequate intake and uptake of the inhalation agent. Following the initial three minutes, decrease oxygen flow to 1–1.5 L/minute and adjust the sevoflurane concentration "to effect.")
- If running sevoflurane 4% or above, look for leaks in the system, improper intubation or inadequate oxygen flow rate.

ILL PETS

Most critically ill pets will not need to be sedated for interosseous catheter placement. If sedation is necessary, use diazepam 0.1 mg/lb IM cats/dogs (maximum dose of 10 mg) plus butorphanol 0.1–0.2 mg/lb (maximum dose of 5 mg) IM. The trochanteric fossa of the femur is the preferred insertion site, but the proximal tibia, or the greater tubercle of the humerus can also be used.

The vaporizer at maintenance levels will normally be set between 2% and 3%. The vaporizer setting and end-tidal sevoflurane concentration are slightly different. Patients that are ill or compromised will often need a vaporizer setting of less than 2%. The goal of gas anesthesia maintenance is to have the patient at a plane of anesthesia that is necessary at any given time. Sevoflurane allows the patient to be taken deeper during the painful part of a surgical procedure, and then taken to a lower plane of anesthesia for closure. The end result is less risk to the patient during anesthesia.

Critically ill patients may be slow to recover from anesthesia. Monitor and document TPR and other vitals frequently and provide supportive care as necessary.

Interosseous catheters may be left in place for up to 72 hours in a critically ill patient. Frequently, they must be pulled within 24 hours if the patient becomes active and bends the needle.

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LOOKING FORWARD – LESSONS AND CONCLUSIONS

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BEST PRACTICES BASED ON OUTCOME ANALYSIS

Quality anesthesia can no longer be defined by "infrequent patient deaths." In an effort to determine what constitutes quality anesthesia, Banfield, The Pet Hospital, has used outcome analysis to evaluate more than 125,000 general anesthetic cases a year. Outcome analysis has indicated that by utilizing practice standards and protocols, standardizing equipment and by implementing a peer review process that promotes continual review of anesthetic practices, a mortality rate of one per 10,000 pets (as close to human quality as possible) is observed. When doctors create unique protocols, the mortality rate increases by four times. In addition to supporting the idea that standardized procedures produce quality anesthesia, outcome analysis has illustrated the following:

- Anesthetic reactions are very rare
- Lack of proper monitoring results in the appearance that patients are alive one minute and dead the next
- Lack of understanding regarding proper drug usage and effects is common
- Development of unique protocols (ie, bypassing standards) increases morbidity rates and mortality rates.

When broadening the discussion of what is included in excellent anesthesia, equipment, patient health status and evaluation (including blood work), drugs and monitoring must all be considered. Regardless of the experience of a doctor, if monitoring equipment is not functioning, an adverse anesthesia event or a fatal outcome can still result. Perfusion must be maintained during anesthesia, and as such, patients that are not monitored have higher morbidity and mortality rates.

PERFUSION BASICS AND PROPER USE OF PREMEDICATION, TRANQUILIZATION, AND IMMOBILIZATION

Adequate perfusion is essential to a successful anesthetic outcome. Evaluating the perfusion of a pet before and during anesthesia is a key component to quality anesthesia management. It is important for the clinician to understand which drugs affect perfusion. Evaluating the perfusion of a patient prior to anesthesia is just one component of the patient evaluation procedure. Within 48 hours prior to anesthetic induction, pre-anesthesia blood work, such as a complete blood count (CBC) with differential and internal organ function screen, should be performed. As always, it is important to review the patient's medical record completely, in addition to performing a thorough physical exam.

After reviewing the results of the CBC with differential and internal organ function screen, as well as conducting a thorough physical exam, determining the most appropriate premedication agents is the next step. Premedications are used to calm the patient, reduce stress, and improve pet handling. Use of proper premedication agents will also decrease the required dose of induction and maintenance agents. The premedication agents used will depend on the health status of each individual patient.

Tranquilization/sedation techniques allow for certain procedures that may include blood collection, otoscopic exams, and may assist in necessary restraint during non-painful procedures. These can also act as anxiolytics. Typically, the patient can still walk, but monitoring the TPR and pulse quality every 15 to 60 minutes is recommended. While tranquilized or sedated, the patient should be under visual observation at all times. The use of an ECG or pulse oximeter can be used at the doctor's discretion. This procedure is recommended for pets over 5 years of age.

Immobilization is typically used for procedures that can be completed in less than ten minutes, are not painful, and do not require general anesthesia. When a patient is immobilized he/she cannot walk and is experiencing a nonsurgical plane of anesthesia. While immobilized, laryngeal and withdrawal reflexes should remain intact. Immobilization techniques may be beneficial for clipping matted hair, radiographs not requiring special positioning, mild ear cleaning, pedicure in aggressive patients, and handling of fractious pets. General anesthesia should be considered in brachycephalic breeds where airway compromise is a concern. Also, pets with excessive pharyngeal folds (Shar pei), or any pet with abnormalities of the pharynx, trachea, larynx and/or esophagus should be maintained under general anesthesia.

SAFE AND EFFECTIVE ANESTHESIA INDUCTION AND MAINTENANCE

Induction methods should facilitate a smooth and calm transition to unconsciousness. However, induction is one of the most common times when adverse anesthesia events occur. In order to prevent adverse events, a complete and deliberate physical examination should be performed on the patient, including a thorough review of the patient's medical record. In addition, a complete CBC with differential, and internal organ function screen should be completed within 48 hours of induction. Ensure that premeds have had 30 minutes to take effect before administering induction agents.

Banfield uses propofol for induction, immobilization and anesthetic maintenance. Telazol can be used when immobilization is necessary and can calm a fractious pet. In addition, this agent can be used as an IV induction agent when lipemia is present. Telazol should not be the first choice with known cardiac disease, but is the safest drug in the Banfield pharmacy for a fractious Pet in the absence of a complete medical history.

Sevoflurane is a newer gas anesthetic maintenance agent. Use of this agent requires a specific sevoflurane vaporizer. Sevoflurane can be used in circle or non-rebreathing circuits. It has similar properties to

Isoflurane, but has some differences. Due to sevoflurane's lower solubility, rapid changes in the depth of anesthesia are possible. This requires close monitoring. With sevoflurane, the return to consciousness is usually rapid. This is especially important in brachycephalic breeds where airway compromise is prevalent. Premedications tend to decrease excitement during recovery.

As always, the three goals of monitoring are to anticipate, recognize and correct complications. Monitoring of the patient's TPR, pulse quality and level of consciousness should be continued until the patient can maintain a sternal position and is fully alert. Anesthetic depth and patient condition are dose dependent. As the anesthetic dose is increased, depth is enhanced and anesthetic safety margins decrease. If uncertain about a patient's anesthetic depth, assume that he/she is too deep. Hypothermia and hyperthermia should also be monitored.

Recovery is also a common time when adverse anesthetic reactions may occur. Continue monitoring TPR, pulse quality and level of consciousness until the patient can maintain a sternal position and is alert. Maintaining a pulse oximeter on the patient will help in this endeavor. Remember to watch for signs of consciousness before removing the endotracheal tube. Signs of increased consciousness include increasing jaw tension, increased swallowing or moving his/her own jaw.

THE PREOPERATIVE PHYSICAL EXAMINTION AND INTERPRETATION OF PREOPERATIVE BLOOD WORK

Prior to any anesthetic procedure, the patient's health should be evaluated. This includes conducting a physical examination (PE) prior to induction, completing pre-anesthetic blood work, which should include a CBC with differential and an internal organ function screen within 48 hours of induction. In addition, the patient's medical record should be thoroughly reviewed and an IV catheter placed. All PE findings should be recorded in the medical record. Based on these comprehensive findings, the best anesthesia protocol can then be selected.

The conditions to review and evaluate during the physical exam include medical history and drug therapy, if the pet has bleeding disorders, hyperthermia, anesthesia problems, shunts, myopathies and pre-existing organ compromise. If illness is detected during the PE, different protocols can be followed that best suit the Pet's individual needs. The physical exam can be divided into the following five categories:

- Assessing capillary refill time and pulse quality
- Evaluating the mucous membranes for adequate perfusion
- Auscultating the heart to assess for cardiac health
- Auscultating the lungs to assess respiratory condition and
- Evaluating the pet's temperature to plan for hyperthermia or hypothermia

BANFIELD EVIDENCE-BASED BEST PRACTICES PET ANESTHESIA FOR HEALTHY, FRACTIOUS, AND ILL PATIENTS

Every pet is unique and some require special consideration prior to anesthesia due to underlying health conditions, breed type (brachycephalic), temperament or organ compromise. Banfield has developed best practices (protocols) as a result of these considerations.

Regardless of the pet's outward appearance, proper evaluation of every pet is necessary prior to anesthesia. A routine CBC with differential and internal organ function screen is performed on each pet. These tests are performed within 48 hours of anesthetic induction.

A few of Banfield's best practices (protocols) include:

- Healthy Pet
- Fractious Pet
- Lipemia
- Abdominal
- Cardiac
- Liver
- Pulmonary
- Emergency Surgery

A fractious pet can be defined as a pet that requires more restraint, a pet requiring more than one attempt at a blood draw or jugular stick because of patient movement, or any pet that shows signs of aggression.

Most critically ill pets will require special treatment that may include interosseous catheter placement, special sedation considerations and extremely close monitoring. Banfield's anesthesia standards and protocols may be adapted to almost any pet with specific health concerns.

MANAGEMENT OF THE ANESTHETIC EMERGENCY

Emergencies are surgical cases that require anesthesia within 15 minutes to save the patient's life. Although outcome analysis has shown that anesthetic reactions are very rare, it is important to work with a team that is prepared for an emergency.

If a patient is in shock, anesthesia is contraindicated. If possible, correct shock prior to induction. If correcting the shock is not possible, mask induction with sevoflurane may be indicated. It is important to minimize stress when utilizing mask induction; if the heart rate increases by 25% or more, allow the patient to relax, then administer the appropriate IV induction agent. Most pets will have a better outcome if stabilized before anesthesia or surgery. In a true emergency, it is important to remember that some premeds used in a healthy pet best practice (protocol) such as butorphanol, may not have had time to take complete effect. Indicators of an emergency include:

- An increase of end tidal CO_2 (>50)
- A decrease of end tidal CO_2 (<35)
- Poor or diminishing pulse quality

- Decreased oxygenation (cyanosis may or may not be present)
- Bradycardia
- VPC

Cardiopulmonary arrest (CPA) can be the natural ending of a full life, or can result due to trauma or disease states. If CPA is due to a potentially reversible traumatic or medical condition, then prompt application of sound cardiopulmonary resuscitation (CPR) techniques, while addressing the underlying cause of the arrest, may allow restoration of life signs.

Effective CPR requires a highly trained, efficient, and coordinated team. This can only result when an effective CPR best practice (protocol) is followed. The goal of Banfield's CPR best practice is to provide an outline for closed chest CPR in dogs and cats. This is a guideline, and to be effective will require training of a team of doctors and nurses on working together efficiently. This protocol only applies to anesthetic cases once cardiopulmonary arrest is noted.

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WHAT ARE THOSE MONITORS TELLING YOU?

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Modern veterinary practice is filled with colorful, beeping monitors designed to aid in monitoring anesthetized patients. The somewhat mistaken idea is that good monitors equate to greater safety. Expensive equipment is only as good as the person evaluating the information. This article is designed to review the commonly used monitors in veterinary practice and help the practitioner decipher what all the beeping/flashing is about.

ELECTROCARDIOGRAM (ECG)

How Does it Work?

The ECG is a recording of the electrical potentials generated by myocardial cells. The potentials produced are small (low voltage), so using conductive gel lowers the skin's electrical resistance, but artifact and poor signal can be a problem. A lead records the electrical signals of the heart from electrodes which are placed at specific points on the patient's body. When a depolarization wavefront moves toward a positive electrode, it creates a positive deflection on the ECG and when a depolarization wavefront moves away from a positive electrode, it creates a negative deflection on the ECG.

What Does it Tell You?

ECGs are useful to assess the rate, the rhythm, and conduction patterns, of the heart. Each complex can also be inspected to look at individual waves (P, QRS, T) and to see they are normally associated and normal size. Abnormal waves can also be identified; which can aid in clinical diagnoses (eg, ventricular premature contractions [VPC], hyperkalemia, or ST segment depression). Although the ECG is only measuring electrical activity, electrical activity is generally associated with a beating heart (big exception: electromechanical dissociation).

Limitations?

The generation of ECG waves does not give ANY information about cardiac output. Normal rhythms may be associated with poor cardiac output and abnormal rhythms (eg, atrial fibrillation) may be associated with adequate cardiac output. Many ECG monitors auto-calibrate the wave size and therefore wave size may be distorted and misleading. Pulseless electrical activity (previously called electromechanical dissociation; EMD) can produce a fairly normal looking ECG rhythm without a heart beat or circulation.

PULSE OXIMETER

How Does it Work?

A pulse oximeter measures the amount of oxygen that is bound to hemoglobin and is reported as a saturation % (SpO_2). Since hemoglobin with oxygen (HbO_2) and hemoglobin without oxygen (Hb) absorb red and infrared light wavelengths differently, the percentage of one form versus the other can be measured. Hb absorbs more visible red light which is why it appears blue. Complex computer programs help identify pulsatile movement (to differentiate from a vein) and calculate the percent saturation. On room air (21% O_2), most mammals have an SpO_2 between 95% and 100%.

What Does it Tell You?

Pulse oximeters are valuable in they provide information about whether the patient has access to oxygen (eg, O_2 tank turned on), whether the patient is breathing, whether the oxygen is exchanging in the alveoli and whether there is enough cardiac output to get the oxygen peripherally as well as generate a pulse at a peripheral site.

Limitations?

The number generated by a pulse oximeter does NOT provide information about whether there is enough hemoglobin to support the patient, but whether the hemoglobin that is there has oxygen attached to it. For example, the ancient cat with a PCV of 9% (Hb of ~3%) probably does not have enough oxygen carrying capacity to supply the body with sufficient oxygen, but the pulse oximeter could easily read 100% saturated. Since many animals are close to 100% saturated on room air, it can be difficult to assess 100% saturation when higher percentages of oxygen are administered. This means you cannot detect a difference between an arterial O_2 of 100 mmHg or 500 mmHg from a pulse oximeter. Although a pulse is required for a reading, a pulse oximeter does not indicate adequate perfusion. Altered hemoglobin (carboxyhemoglobin or methemoglobin) will alter the accuracy of SpO_2 readings. Methemoglobin will cause the SpO_2 to read 85% and carboxyhemoglobin generally gives a falsely high reading in patients with CO poisoning.

BLOOD PRESSURE

Blood pressure is often used as an indirect measure of cardiac output (CO) and organ perfusion and clinically can be measured in three ways: Doppler, oscillometric, and direct (invasive).

How Does it Work?

Doppler: A Doppler probe can be used by finding an audible peripheral pulse; inflating a sphygmomanometer cuff to occlude flow to that vessel; slowly deflate the cuff until the audible pulse is heard again. The pressure at which the pulse resumes is the systolic pressure. There is some evidence that in cats; blood pressure measured this way is somewhere between mean and systolic pressure.[1]

Oscillometric: Automated blood pressure monitors use a cuff that measures changes in oscillations. The cuff is inflated until the pulse is occluded (no oscillations); the cuff is slowly deflated until the pulse generates oscillations again (that is systolic pressure).

The point of maximal oscillations is the mean blood pressure and the diastolic is usually calculated from the other two values. Anything that can change oscillation (eg, shivering) can negatively affect accuracy.

Direct: For invasive (direct) blood pressure. A catheter is placed into a peripheral artery and connected to a pressure transducer. The transducer can then generate an arterial wave (graphically) and measure systolic, mean and diastolic pressure.

What Does it Tell You?

Depending on the method used, blood pressure monitoring will give you at minimum a systolic blood pressure and often a mean and diastolic blood pressure. Although somewhat oversimplified, systolic pressure is most reflective of cardiac output and diastolic pressure is most reflective of vessel tone. Mean blood pressure is the best indicator of organ (especially renal) perfusion.

Limitations?

Although higher blood pressure is usually associated with increased cardiac output and increased perfusion; that will **NOT** be true with big changes in systemic vascular resistance (SVR). For example, a patient administered medetomidine will initially vasoconstrict and have a decrease in CO. In that patient, the blood pressure will rise with a decrease in CO.

Accuracy is best with direct pressure measurement, followed by Doppler and then oscillometric. Accuracy of an oscillometric is based on many things; appropriate size of cuff, shape of leg, heart rate and rhythm. It is not surprising that accuracy could be different in a Bulldog leg versus a Retriever leg.

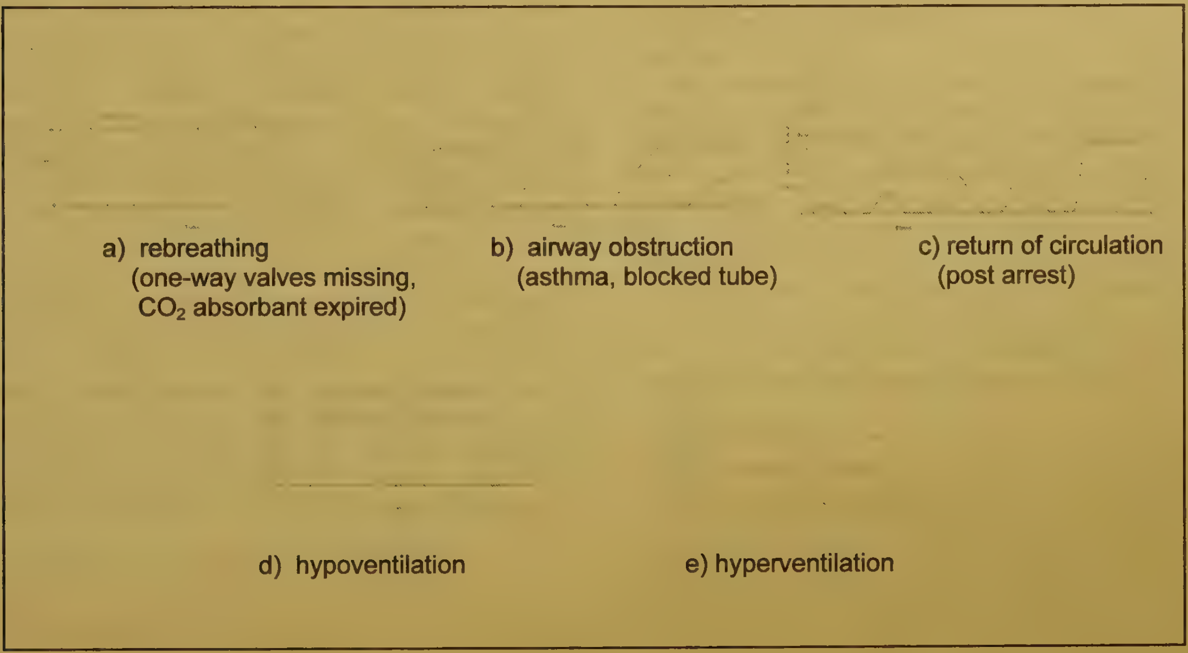
CAPNOGRAPH

How Does it Work?

A capnogram or capnograph is an indirect measure of ventilation. It measures the amount of carbon dioxide (CO_2) in the breath at the end of expiration ($ETCO_2$). Since CO_2 easily moves across the capillaries and alveoli, the assumption is made that the amount of CO_2 at the end of the breath (end-tidal volume) is equivalent to the CO_2 in the blood. In healthy awake animals the difference between the arterial and end-tidal measurements are indeed close (~5 mmHg different). Therefore, capnography allows us to estimate ventilation based on the CO_2 in the breath. The amount of CO_2 in exhaled gas is measured by a comparison with a reference gas for the absorption of infrared light. By plotting the amount of CO_2 exhaled over time, a capnogram can be generated (a graphic representation). The size, upper and lower limits, and shape of the capnogram is quite useful in clinical diagnoses of respiratory as well as mechanical problems.

What Does it Tell You?

Machines that just give an $ETCO_2$ number provide information about ventilation and indirectly cardiac output. If there is insufficient cardiac output to bring the CO_2 to the lungs, then the amount exhaled (even with normal ventilation) will fall. Machines that provide a waveform (capnograph) provide a lot of information about the patient (Figure 1). Inspection of the waveform can give information about the airways (eg, asthma), whether there is a leak in the system (machine or ET cuff), whether there is rebreathing of CO_2 (eg, CO_2 absorbant has expired, or one-way valves are not functioning).



a) rebreathing (one-way valves missing, CO_2 absorbant expired)

b) airway obstruction (asthma, blocked tube)

c) return of circulation (post arrest)

d) hypoventilation

e) hyperventilation

Figure 1. Examples of capnographs.

Capnographs are very useful in arrest situations, as they can indicate successful cardiopulmonary resuscitation (CPR) as well as the return of spontaneous circulation.

Limitations?

Capnography is based on the idea that the end-tidal CO_2 concentration reflects the arterial CO_2 concentration ($PaCO_2$). Although this is true in healthy, awake patients, the difference between the $ETCO_2$ and $PaCO_2$ can become increased with disease (eg, pulmonary thromboembolism), anesthesia, or positioning. The ONLY true was to know arterial CO_2 is to measure it (blood gas).

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ANESTHESIA PROTOCOLS FOR CHALLENGING CANINE CASES

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The variety and complexity of patients seen by veterinarians today are increasing. Many practitioners will be presented with patients for anesthesia that will require them to deviate from their standard anesthetic protocols. This goal of this article is to help the practitioner formulate anesthetic protocols for challenging cases using drugs they likely have in their practice (and/or possibly encourage them to try some new ones).

WHAT MAKES FOR A CHALLENGING CANINE CASE?

Most veterinarians consider a dog a challenge to anesthetize if it has a disease process that might or does interfere with the delivery of anesthesia. Every patient deserves an individual anesthetic protocol, vigilant monitoring, and venous access. However, due to cost and time, many animals are anesthetized in a "routine" way with great success. For those patients who fall outside the routine, it is important to think through the disease process, evaluate the status of the individual patient, have venous access, and monitor the physiologic effect on your patient.

Goal?

The goal of anesthesia is to provide unconsciousness and amnesia while maintaining perfusion of vital organs (brain, kidney, heart, etc.). Adequate perfusion is not just the supply of liquid through the vessels, but providing oxygen and glucose (oxygen delivery). If we recall, energy in the body is supplied by oxidative phosphorylation (aerobic metabolism). The ever important oxygen molecule is necessary for the production of energy in the form of ATP. The ATP is then used to maintain normal physiologic functions (eg, maintaining cellular gradients, protein synthesis, etc.). Cells can produce energy without oxygen (anaerobic metabolism) only on a small scale which is insufficient to maintain an entire body. Furthermore, the by-product (lactate) of anaerobic metabolism contributes to academia (lactic acidosis). Ultimately, without oxygen and the substrates it uses to phosphorylate (glucose, fats) cellular function cannot continue and the body will die. In the author's opinion the majority of patient death under anesthesia is due to the **sequela of poor perfusion and/ or oxygen delivery**.

WHAT ARE SOME THINGS I CAN AFFECT?

Oxygen

Supplemental oxygen is often overlooked as a treatment tool. Remember that room air is ~21%. That means by supplementing oxygen by a face-mask (giving 100% oxygen), you can increase available oxygen four to five times. Normally the VAST majority of oxygen is carried on hemoglobin and only a small portion is dissolved in the plasma (0.3%). However, in anemic animals, if you supply 100% oxygen, the fraction dissolved in the plasma can be a greater percentage (almost 20%) of the total oxygen and provide needed support.

Blood

Anemic patients (packed cell volume [PCV] <20%) who are to be anesthetized should have their oxygen carrying capacity supplemented with red blood cells (whole blood or packed red blood cells) or with hemoglobin (Oxyglobin®) before anesthesia. Anemic patients that are stable awake can quickly become unstable when anesthetized (due to drugs/loss of sympathetic tone/loss of autonomic reflexes).

Volume

Hypovolemic patients should ideally have volume replacement/ resuscitation before anesthesia with crystalloid and/or colloidal solutions. Similar to anemic patients, hypovolemia can be exacerbated under anesthesia due to drugs effects, loss of sympathetic tone, and loss of autonomic reflexes.

Cardiac Output

It is often helpful to identify the cause of low cardiac output (CO). Remember that cardiac output can be influenced by preload (volume returning to the heart), afterload (systemic vascular resistance) and cardiac contractility. Thus it is useful to know from a treatment perspective if cardiac output is being adversely effected because the patient is hypovolemic or inappropriately vasodilated (eg, in shock), or both.

CONSIDERATIONS FOR PARTICULAR CHALLENGING CASES

Aggressive Dog

Aggressive dogs are a danger to everyone in your practice (as well as you) and the sooner they can be chemically restrained, the better it is for everyone. In these dogs it is important that all the medication can be administered with one syringe (ID—intra-dog). Drugs that require large volumes or intravenous (IV) access are not useful. For full chemical restraint, my preference is a mixture of medetomidine and ketamine; medetomidine at 10–20 µg/kg + ketamine 5 mg/kg. Prudence must be used for dogs where alpha-2 agonists are contraindicated (eg, heart disease, hypovolemia).

Cesarean Section

Pregnancy puts a great strain on the dam. Maternal plasma volume almost doubles (a lot of volume for a heart to pump) and decreases in functional residual capacity leaves less respiratory reserve. Most C-section patients are emergent and both the mother and puppies may be compromised. Ideally, puppies should enter the world without any drugs. Unfortunately, almost all drugs that pass the blood brain barrier to anesthetize the dam also cross the placenta and effect the puppy. Therefore, whenever possible, the dam should have no premedicants. The ideal induction agent would provide for a rapid induction and would be easily and quickly metabolized. Although pre-emptive analgesia is always preferred, this is one of the few exceptions where it is prudent to wait until the puppies are delivered to administer an opioid. Some theriogenologists recommend no opioid analgesia so that dam or puppies do not become sedated. Following an abdominal procedure, opioid analgesia is appropriate; however, it might be reasonable to choose a partial agonist to minimize the side effect. NSAIDs are routinely used in the human post delivery period and as long as the dam is clinically healthy and hydrated there is no reason not to do the same.

A large volume of fluid is lost during delivery and many dogs will not drink water during labor. Therefore, all C-section patients should be administered IV crystalloid fluids.

The hypoventilation seen while awake is only exacerbated with anesthesia and dorsal recumbency. These dogs should have their ventilation assisted.

Sample Protocol: IV catheter + fluids; No premedication; Induction with propofol 6 mg/kg IV to effect. Maintenance with isoflurane/ sevoflurane in oxygen (sevoflurane may allow for quicker arousal of puppies). After puppies are delivered the dam should be provided analgesia (eg, buprenorphine 0.02 mg/kg IV, and carprofen).

Drugs to Avoid: Xylazine has been shown to increase the morbidity and mortality of both puppies and dams, likely due to the decrease in cardiac output and decrease uterine blood flow. It is reasonable to avoid other alpha-2 drugs as they would likely produce a similar effect. Human babies are slower to wake up after the moms are administered thiopental (compared with propofol).

Gastric-Dilatation-Volvulus (GDV)

Most dogs with GDV present dehydrated and with poor venous return due to the enlarged stomach. Similarly, they often present hypoventilating due to pressure on the diaphragm. These patients need aggressive fluid therapy and benefit from supplemental oxygen (eg, face-mask). It is important to choose anesthetic drugs that do not worsen the cardiovascular status; that is not decrease cardiac output further either by myocardial depression or vasodilation. After induction of anesthesia, ventilation should be assisted; this can be as sophisticated as a positive pressure ventilator, or from the willing hands of a kennel kid.

Patients who do not respond to aggressive fluid therapy (crystalloids, colloids) may need inotropic support (dopamine or dobutamine) to maintain adequate blood pressure. GDV patients are also often arrhythmic; particularly with ventricular arrhythmias, so lidocaine may be needed for less productive rhythms. (Lidocaine constant rate infusions (CRIs) can be used for adjunctive analgesia as well as antiarrhythmics.)

Sample Protocol: Sedation with hydromorphone 0.01 mg/kg +/- midazolam 0.3 mg/kg IV, IM, SQ (this is often enough to pass a stomach tube for GDV). Induction with midazolam 0.2 mg/kg + propofol 6 mg/kg (to effect). Alternatively, midazolam 0.2 mg/kg + etomidate 2 mg/kg (to effect) can be used. (The midazolam allows for smaller amounts of propofol or etomidate to be used during induction.) Ketamine would be considered an acceptable agent as long as the dog is not severely tachycardic or arrhythmic. Maintenance of anesthesia can be with either isoflurane or sevoflurane. Since both inhalants cause vasodilation, additional analgesia from a CRI of opioid (eg, fentanyl, MLK) or from intermittent boluses can help decrease the amount of inhalant needed. In addition, rehydration, inotropes as needed, and antiarrhythmics as needed.

Drugs to Avoid: Since maintaining blood pressure/ perfusion is vital, drugs that decrease cardiac output or blood pressure should be avoided; alpha-2 agonists (medetomidine), acepromazine, and thiopental.

Brain Tumor

The two major concerns of anesthetizing a patient with a brain tumor are elevated intracranial pressure (ICP) and seizures. Using drugs that are anticonvulsant (eg, benzodiazepines, propofol, thiopental) are wise, as are avoiding drugs that potentially lower the seizure threshold (eg, ketamine, acepromazine?). Similarly, drugs that decrease ICP (thiopental, propofol) should be chosen and drugs that increase ICP (ketamine) should be avoided.

Thiopental and propofol have very favorable CNS pharmacodynamics; they both make the EEG isoelectric (flat), decrease cerebral blood flow, and decrease intracranial pressure. The decrease in EEG waves decreases the glucose and oxygen demands of the brain, and the decreased blood flow decreases ICP. Interestingly, propofol has been shown to maintain cerebral autoregulation during surgery. This fact, the rapid elimination, and lack of accumulation with a constant rate infusion have made propofol my induction drug of choice with CNS disease.

Intracranial pressure can also be affected by CO_2 levels. Elevation of CO_2 (hypoventilation) causes a linear increase in ICP, whereas a decrease in CO_2 will decrease ICP. Anesthesia and some sedative/ analgesics can cause hypoventilation and thus increase ICP (in compromised animals). Therefore. modest hyperventilation ($PaCO_2$ ~35) is recommended for patients with space-occupying lesions while anesthetized.

Sample Protocol: Sedation with butorphanol (0.4 mg/kg). Induction with propofol (6 mg/kg to effect). Maintenance with isoflurane. Hyperventilation while anesthetized. If a painful procedure is planned, a stronger opioid can be used AFTER induction and ventilation is controlled.

Drugs to Avoid: Avoid any drugs that increase ICP (ketamine). Be cautious with drugs that decrease ventilation (increase CO_2) such as pure mu-opioids (eg, morphine, hydromorphone).

Liver Shunt

Dogs with blood shunting around the liver generally have low albumin, low clotting factors, and metabolize drugs more slowly. Often these are young, underweight animals and some present with seizures. When anesthetizing these dogs, it is important to choose drugs that have minimal or alternative liver metabolism (eg, propofol) and avoid long-acting drugs with exclusive liver metabolism (acepromazine). Since albumin levels in these dogs are generally low, drugs that extensively protein bound may have exaggerated effects and oncotic pressure may be low which can lead to hypotension.

Although opioids are liver metabolized, they are good choice in shunt dogs. Opioids provide sedation and analgesia and can be reversed if needed. Midazolam is another good choice as it is water soluble (valium is in propylene glycol), short acting and can also be reversed. Propofol does have some hepatic metabolism, but also has extensive extrahepatic metabolism; as metabolism exceeds hepatic blood flow. In fact, the pharmacokinetics of propofol are virtually unchanged in pigs undergoing liver transplants.

Sample Protocol: Sedation with hydromorphone (0.1 mg/kg). Induction with propofol (6 mg/kg IV to effect). Maintenance with isoflurane. Non-lactate (less for the liver to metabolize) containing fluids. Plasma/ albumin PRN for hypoalbuminemia.

Drugs to Avoid: Acepromazine, thiopental, diazepam

Laryngeal Paralysis

Dogs that present with laryngeal paralysis are often elderly, overweight, and distressed. Before a laryngeal exam, surgery (or referral) can be made the dog must be stabilized. Decreasing the panic and slowing the respiratory rate often helps. Supplemental oxygen can help as long as the face-mask or flow-by does not distress the dog. Dogs that have been working hard to breathe are at risk. They generally have a respiratory acidosis and can suffer respiratory fatigue. For moderately stable dogs, sedation and oxygen therapy will result in a vast improvement. For unstable dogs, they need to be quickly anesthetized, intubated/ tracheostomy and assist their breathing. Use caution with sedative that can increase panting or decrease ventilation (eg, pure mu opioids—morphine, hydromorphone).

Sample Protocol: Sedate with acepromazine, +/- butorphanol 0.2 mg/kg and provide supplemental oxygen. Induction with propofol (6 mg/kg IV to effect) or valium-ketamine. Quickly intubate. Maintain with isoflurane or sevoflurane. Pay attention if the animal is too tired to breathe for itself.

Drugs to Avoid: Avoid pure mu-opioids until airway has been established. Do not mask down with an inhalant (too slow control of airway).

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MORPHINE-LIDOCAINE-KETAMINE (MLK)

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WHAT IS MLK?

MLK is a solution containing morphine, lidocaine, and ketamine. It is generally delivered as a constant rate infusion (CRI) either during or following surgery.

Morphine is a pure mu-opioid agonist that works by inhibiting ascending nociceptive information by decreasing neurotransmitters (eg, acetylcholine, dopamine, substance P, and norepinephrine).

Lidocaine is a local anesthetic that interrupts the pain pathway by blocking sodium channels and preventing transmission of neuronal impulses.

Ketamine is dissociative anesthetic that disrupts cortical perception of pain and interrupts central sensitization at the level of the dorsal horn of the spinal cord.

WHAT ADVANTAGE DOES IT POSE?

MLK is used to provide balanced analgesia, decrease the amount of inhalant administered, and potentially decrease central sensitization (wind-up). Pain is better controlled when the pain pathway is interrupted/ attenuated in different ways. The three drugs work synergistically and allow for smaller doses of each to be administered. In addition, by providing sedation and analgesia, the combination allows for slower, more comfortable patients in the early postoperative period, particularly with anxious patients or following painful procedures (eg, fracture repair, ear canal ablations, etc). The MAC sparing effects can also provide hemodynamic stability by decreasing the amount of inhalents that are required.

HOW DO I MAKE IT UP AND DELIVER IT?

To quote a non-veterinary proverb: There is more than one way to skin a cat.

The original paper by Muir et al described adding the three drugs to the maintenance fluids and administering at the generic 10 mL/kg/hr while anesthetized. From that paper it is recommended that 10 mg of morphine, 150 mg of lidocaine, and 30 mg of ketamine be added to 500 mL bag of crystalloid fluid and administered at 10 mL/kg/hr. The limitations of this method are that such high fluid rates are rarely used postoperatively, and the fluid rates during anesthesia cannot be altered without altering the drug administration rates. In addition, there is not scientific evidence that the ratio of drugs chosen for that study is ideal and non-alterable. Moderate changes have been suggested and used successfully.

Wetmore suggests that the CRI be administered at 2 mL/kg/hr, thus the solution should be made by adding 60 mg morphine, 750 mg lidocaine, and 150 mg ketamine to a 500 mL bag of fluids. At these concentration and delivery rates: morphine at 4 µg/kg/min (0.24 mg/kg/hr), lidocaine at 50 µg/kg/min (3 mg/kg/hr), ketamine 10 µg/kg/min (0.6 mg/kg/hr).

Alternatively, Stein recommends a solution delivered at 1 mL/kg/hr with a solution made by adding 60 mg morphine, 500 mg lidocaine, and 60 mg ketamine to a 500 mL bag of fluids. Given these concentrations and delivery rate; morphine would be delivered at 2 µg/kg/min (0.12 mg/kg/hr), lidocaine at 17 µg/kg/min (1 mg/kg/hr) and ketamine delivered at 2 µg/kg/min (0.12 mg/kg/hr).

CLINICAL CONCERNS

Clinically, it is important to realize that higher morphine dosing may result in slower recoveries and potentially oversedated patients. The parenteral dose range for morphine is quite large (0.1–0.9 mg/kg q 4–6 hr). Since I generally administer morphine at 0.5 mg/kg q 4–6 hrs to a dog....both protocols above fall into a clinically appropriate dose (one a little higher and one a little lower). Based on toxicity studies, lidocaine administration should not exceed 8 mg/kg q 20 minutes (24 mg/kg/hr). Thus, none of these protocols even approaches toxic levels in a dog. All the ketamine doses are far below the anesthetic dose of ketamine (5 mg/kg) and it is highly unlikely that any behavioral (dissociative) effects would be seen.

CAN I USE IT IN CATS?

All the drugs used in the combination can be safely administered to cats. However, constant rate infusions (CRI) of lidocaine in cats are not recommended as the CV depressive effects are greater than the MAC sparing effects. Therefore, lidocaine can either be omitted or administered at smaller doses.

HOW DO I LOG THE CONTROLLED DRUGS?

Most clinicians find making up 500 mL wasteful in small patients because the morphine has to be associated and signed out with a particular patient. Alternatively, the same ratio of drug can be formulated in smaller quantities (50 mL or 100 mL) based on the size of the patient and how long you expect to deliver the CRI (eg, just during surgery, or over 24 hours).

POSNER'S PREFERENCE?

Analgesic requirement can change vastly from patient to patient and from disease to disease. I prefer to run my opioid CRI independently, so that I may adjust the rate of the opioid as needed. This also makes controlled drug balancing easier.

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BUTORPHANOL OR BUPRENORPHINE: WHICH SHOULD I USE?

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OPIOIDS

Opioids are the mainstay of analgesia in human and veterinary medicine. There are at least three different types of opioid receptors; mu (μ, OP3), kappa (κ, OP2), and delta (δ, OP1). The previously described sigma (σ) receptor is now considered an NMDA receptor. Presently, only the mu and kappa receptors are clinically manipulated for analgesia. Opioid receptors are widely distributed in the brain, the spinal cord, and peripherally. However, the distribution, density, and even type of receptors vary between species. Binding of opioids to opioid receptors provides analgesia primarily by decreasing neurotransmission (presynaptic inhibition of neurotransmitters, eg, acetylcholine, norepinephrine, substance P, dopamine). This results in hyperpolarization of afferent neurons and thus diminished ascending nociception.

BUTORPHANOL

Butorphanol is a mixed opioid agonist/antagonist. It is an agonist at the kappa receptor and antagonist (really a weak agonist) at the mu receptor. Kappa receptor activation provides mild to moderate analgesia, but less side effects than pure mu opioids. Respiratory and CV depression are minimal; there is less nausea and vomiting, and generally less dysphoria. The analgesic effects of butorphanol have a ceiling effect at ~0.8 mg/kg; where increasing the dose will not increase the opioid effect. Analgesic and sedative effects can be enhanced when given with other CNS depressants (eg, alpha-2 agonists, phenothiazines). Butorphanol is also used as an antitussive.

At clinically relevant doses (0.2–0.4 mg/kg) (IM or IV) butorphanol has a rapid onset of action, but the duration of action in dogs and cats is generally considered less than 1 hour. However, some recent work has shown that individual cats may be provided analgesia for up to 5 hours! Alternatively, butorphanol may also be administered as a constant rate infusion (CRI). Butorphanol administered as a CRI in horses has been shown to be an effective analgesic and actually decreased the duration of hospitalization following colic surgery. There appears to be huge individual patient variability as to potency and duration of action. Therefore, patients administered butorphanol should be routinely assessed for pain.

Behaviorally, cats sedate well with and appear to have a sense of well being following administration of butorphanol.

The effectiveness and duration of oral butorphanol are unknown (unpublished). Some pilot data (also unpublished) indicates the bioavailability at ~10% to 30%.

Butorphanol is a Schedule IV controlled drug, which requires a DEA license as well as controlled access (lock-box) and logbook.

Cost: Butorphanol is supplied as a 1, 2, or 10 mg/mL solution. At clinically relevant doses (0.2 mg/kg of the 10 mg/mL concentration), current (2007—100 mg for ~$50) prices relate to a ~$0.10/kg cost to the veterinarian. Therefore a 0.2 mg/kg dose in a 5-kg cat would be ~$.50 and a 50-kg dog would be ~$5.00.

BUPRENORPHINE

Buprenorphine is a partial mu-agonist and kappa receptor antagonist. It is an interesting drug in that it has a very strong binding affinity, which translates in to a longer duration of action than most other opioids (up to 8 hours). Since it is a partial mu-agonist, buprenorphine has a ceiling effect, so after reaching the ceiling, increasing the dose will not increase the clinical effect. Buprenorphine causes fewer side effects (respiratory, cardiovascular, emesis) than the pure mu-opioids. Side effects may be exacerbated when given with other CNS depressants (eg, alpha-2 agonists, acepromazine).

Buprenorphine can be administered SQ, IM, IV, although time to full effect is generally slower than with other opioids (~30 minutes). Buprenorphine may be administered transmucosally (not orally) in cats due to the high pH (~8.5) of the cat mouth. A dose of 0.1 to 0.2 mg/kg transmucosally will produce similar plasma levels to IV dosing. Recently, buprenorphine patches (transdermal) were assessed, but did not provide analgesia in thermal testing models.

Cats also have favorable behavioral effect with buprenorphine, but rarely become significantly sedated. Interestingly, buprenorphine did not change MAC in cats (which may support that idea that doesn't provide great CNS depression).

There appears to be huge individual patient variability as to potency and duration of action. Therefore patients administered buprenorphine should be routinely assessed for pain.

Buprenorphine is a Schedule III controlled drug, which requires a DEA license as well as controlled access (lockbox) and logbook.

Cost: Buprenorphine is supplied as a 0.3 mg/mL solution. At clinically relevant doses (0.02 mg/kg), current (2007—3 mg for $34) prices relate to a ~$0.20/kg cost to the veterinarian. Therefore, a 5-kg cat dose would be ~$1.00 and a 50-kg dog would be ~$10.00.

BUTORPHANOL + BUPRENORPHINE

Some clinicians administer both drugs in an effort to activate both mu and kappa receptors and to provide both fast onset of action and a long duration of action (Table 1). A recent study in cats, where clinically relevant doses were used, did not show a significant synergistic effect (compared with either drug alone). Interestingly, one could argue that combining the drugs could also provide antagonism at both the mu and kappa receptors.

Table 1. Comparison of Butrophanol and Buprenorphine

	Butorphanol	**Buprenorphine**
Receptor agonist	K-agonist	Mu-agonist
Receptor antagonist	Mu-antagonist	Kappa-antagonist
Dose range	0.1–0.4 mg/kg	0.01-0.02 mg/kg
Time to effect	5–10 minutes	<30 minutes
Duration of action	45 min–5hrs?	Up to 8 hrs
Cost at relevant dose	~$0.10/kg	~ $0.20/kg

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EPIDURAL ANESTHESIA AND ANALGESIA: CLINICAL APPLICATION FOR ROUTINE SURGICAL USE

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Epidural anesthesia and analgesia is frequently over looked as an adjunct to routine anesthesia and analgesia protocols. Epidurals are initially daunting to perform but with some experience, they can be performed in minutes but veterinary and technical staff in most hospital settings. The primary benefit of epidural anesthesia is the potential to decrease the level of inhalant anesthesia required to maintain the patient while performing a specific surgical procedure. We use epidurals for the majority of rear-limb orthopedic cases, perineal surgery, and caudal abdominal surgery. The addition of morphine to the epidural provides additional analgesia in these cases as well as other cases reaching as far forward as the forelimb.

ANATOMY

The epidural space is the space between the bony spinal column and the spinal cord. It is easily accessed in the caudal aspect of the spinal column and there is minimal risk of injury to the spinal cord at this level. The injection site is between L6-L7 or L7-S1. This is easily identified as the area of the spine between the ilial wings. If you draw a line from one ilial wing to the other and a second line tracing the spinal column, the two lines will bisect over the site for your epidural injection.

EQUIPMENT

Minimal equipment is required for epidurals. A selection of spinal needles should be available; 20g needles of various lengths (1½, 2½, and 3½) would cover more than 95% of small animals. An 18-gauge, 3-inch needle can be used but a 20-gauge 3½-needle can easily substitute. Sterile gloves, a sterile drape, and appropriate epidural agents round out the list.

TECHNIQUE

Aseptic technique is required when performing epidurals. The area around the injection site is clipped (a rough square that is 2 to 4 inches wide in most animals) and prepared with an antiseptic solution. A fenestrated drape (disposable material, sterile surgical towels or plastic adhesive drapes) is placed to cover the area and provide a wider sterile field for the person placing the spinal needle. (Experienced individuals may choose to dispense with the drape as they become confident with the procedure.) The animal is placed in either lateral or sternal recumbency; the positioning is strictly a preference for the individual who is performing the epidural.

Place the fingers of your left hand (non-dominant) on each ilial wings and drop a middle finger directly over the spinal column. Normally, there is a slight depression at this location, representing the space between the spinous processes of L7 and S1. This is the site for initial penetration of the spinal needle.

Insert the spinal needle into the depression and advance it to the bone of the spinal column. Stop at this point and check the orientation of the needle to make sure it is in-line with the spinal column. Slowly walk the needle in cranially or caudally until it "pops" through the interosseous ligament into the spinal canal. The needle is advanced to the ventral aspect of the canal. At this time, you may notice a "tail twitch" in the dog.

Remove the stylet from the spinal needle. Check to see if any cerebrospinal fluid (CSF) escapes from the needle, indicating that you have entered the subarachnoid space. In the event that you have entered the subarachnoid space, you should either 1) reposition the needle in a more caudal intervertebral space or 2) reduce the volume given by 50%. Another technique for checking the needle position is to inject a small amount of air (<3 mL) through the needle. If the needle is in position in the epidural space, there will be no resistance to the injection of the air. If the needle is not in the proper position, there will be resistance to the injection and the plunger of the syringe will bounce back. In this case, replace the stylet and reposition the spinal needle.

Once the spinal needle is properly positioned, slowly inject the desired medication into the epidural space. The direction of injection can be manipulated by turning the needle's bevel in a cranial or caudal direction. For orthopedic surgeries, placing the leg to have surgery in a dependent position for 10 minutes after injection is supposed to concentrate the anesthetic over the nerves to that leg. After you have completed injecting the anesthetic or analgesic into the epidural space, remove the needle and resume preparing the patient for surgery.

FINAL CONSIDERATIONS

Numerous medications have reported for epidural administration. However, there are a few considerations when thinking about epidural anesthesia or analgesia.

- Most references recommend limiting the total volume to 6 mL total. I have given larger volumes without any adverse effects; however, I would recommend heeding this recommendation when beginning to perform epidurals.
- If I am combining an anesthetic and an analgesic in a single injection, I give the analgesic first. The thought process is if I am advancing one of the agents by injecting the second agent, I would prefer to advance the analgesic cranially rather than the anesthetic.
- Whenever possible, use drugs formulated specifically for epidural administration. Giving medications that have preservatives in the formulation have been linked to local inflammation of the spinal cord in humans. While I have not encountered a problem, we use preservative-free epidural preparations for the majority of our epidurals.

- Epidurals can add flexibility to your anesthetic and analgesic protocols. Gaining comfort takes a short period of practice and a proper understanding of the techniques. Try it and you'll be pleased with the results.

Table 1. Epidural Agents

Drug	Dosage Dog (mg/kg)	Dosage Cat (mg/kg)	Onset/ Duration	Comments
Morphine a. Astromorph PF b. Duramorph 0.5 mg/mL	0.1 mg/kg (1 mL/10 lb)	Same	30–60 min/ 12–24 hrs	In early operative period **do not** rely on epidural anesthesia. Premedicate with appropriate complimentary opioid. If CSF, remove and replace or reduce dose by 50% (also reduces duration) Affects only sensory nerves; does not provide significant muscle relaxation
Buprenorphine 0.3 mg/mL	0.003–0.006 mg/kg; add volume up to 0.3 mL/kg	Same	30 min / 12–24 hrs	See above
Lidocaine HCl 2.0% (20 mg/mL)	0.22 mL/kg 1 mL/10 lb	Same	5 min / 60–90 min	Monitor anal tone to assure effectiveness Elevate head first 10 minutes = Place "operated leg" down for 10 minutes Place in dorsal if bilateral or tail procedure Affects motor and sensory nerves
Bupivacaine 0.5% (5 mg/mL)	0.22 mL/kg 1 mL/10 lb	Same	20–30 min/ 4–6 h	May sting in awake or sedated patient Takes a while to see lack of anal tone

INTRODUCTION TO SMALL ANIMAL ANESTHESIA BEST PRACTICES BASED ON OUTCOME ANALYSIS

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Anesthesia in the pet practice has always been one of the more challenging and complex procedures that a practitioner performs, and yet, it is done every day with hardly a second thought. Even more challenging is the wide variation of anesthesia practices used by different doctors. If the question is asked to the many doctors who join Banfield, "Why is there a wide variety of anesthesia practices/protocols being utilized in general practice today?" one common theme comes to the forefront. Every school knows that a wide variety of practice methods currently exist, and as such, they want to expose students to the many variations of practice. This results in no standards of practice for the general practitioner regarding anesthesia. Should the veterinary schools be relied upon to set the standards for general practitioners? The caseloads of most of the veterinary teaching hospitals are referrals, and as such, do not reflect the typical pet practice.

When considering an anesthesia training methodology, a deeper question should be asked which is, "How do you determine quality for anesthesia?" The answer starts with outcome analysis, which helps determine whether the results are better with one method versus another. If practitioners agree that improved case outcomes are a good measure of quality for anesthesia, and a standard method of anesthesia results in improved case outcomes, then anesthesia quality has been improved. Better quality is positive for the profession as a whole.

Banfield's anesthesia standards and protocols are a result of this thinking. The question that I posed in 1998 was, "Can an anesthesia method be developed that would decrease the mortality rate (as well as other adverse case outcomes associated with anesthesia) not only for one hospital, but for hundreds of hospitals?" The challenge forced the question, "Is anesthesia an 'art' or a 'science'?" If it is art, then the mortality rate is based on luck and experience. If it is science, then many aspects of anesthesia should be repeatable with standardized methodologies.

Banfield has the luxury of evaluating more than 125,000 general anesthetic cases a year. By utilizing practice standards and protocols, standardized equipment, and ongoing outcome analysis (the ongoing outcome analysis is part of the peer review process—a concept taken from human medicine), a constant process of improvement through learning from ongoing experience occurs. Peer review, combined with standardized software and equipment, has the benefit of removing many of the variables seen by the profession, and has resulted in marked improvements for Banfield regarding anesthesia case outcomes.

The result of all of this has shown that anesthesia is much more of a science than an art form, therefore forcing practitioners to review their entire approach to anesthesia. Science often requires that old habits of practice change, even if it doesn't feel right, and forces a paradigm shift. Science may require doctors to change, and change is often difficult. This requires practitioners who have a method they would like to stay with, because of habit, or because it just "feels right," to justify with a medical reason, the superiority of the status quo. It is no wonder that many argue against change, but change is upon us.

MEASURING QUALITY ANESTHESIA

Quality anesthesia can be measured by a number of different methods. The first method chosen by Banfield was mortality rate. All anesthesia deaths are taken through the peer review process, and many of these cases also have necropsy results. This provides consistent data on a large enough sample size to identify many patterns that affect mortality. The same factors that affect mortality also affect morbidity; and as such, reducing one will reduce the other.

Research studies regarding anesthesia methodologies and case outcomes in the profession are rare. A study performed with 250 small animal practices in Canada, in which all used isoflurane as the standard, showed a mortality rate of approximately 1 death per 1000 anesthetic procedures. It is a reasonable assumption that in the US, the average small animal veterinary practice is no different, although to my knowledge, no research studies have surfaced. Some have suggested that the mortality rates for general anesthesia in rescue shelters, using injectable anesthesia and minimal monitoring, is as high as 1 per 100. A study by the US Army Veterinary Corps was completed reviewing all deaths and euthanasias of 927 military working dogs from 1993 to 1996, including anesthetic deaths. Anesthetic arrest was noted in 10 of the 927 dogs, or a rate of approximately 1 per 100 patients.

The goal of our protocols is to be as close to human quality as possible (mortality rate of 1 per 10,000). Based on the peer review process, we were able to determine that when the protocols are followed, the mortality rate is approximately 1 per 10,000. These findings were based on case reviews during a time period during which 69,000 procedures were performed. When doctors created unique protocols, the mortality rate increased by 4 times. At a mortality rate of 1 per 10,000 procedures, a doctor averaging 4 general anesthetic procedures per day, and working 220 days per year, would have on average one fatal complication every 11.4 years. It clearly is exciting to have a system that potentially will allow more than 10 years between fatal events.

"Infrequent patient deaths" might have been considered successful in the past but can no longer be labeled as quality anesthesia today. Our goal should be for the patient's condition to be equal or better than the

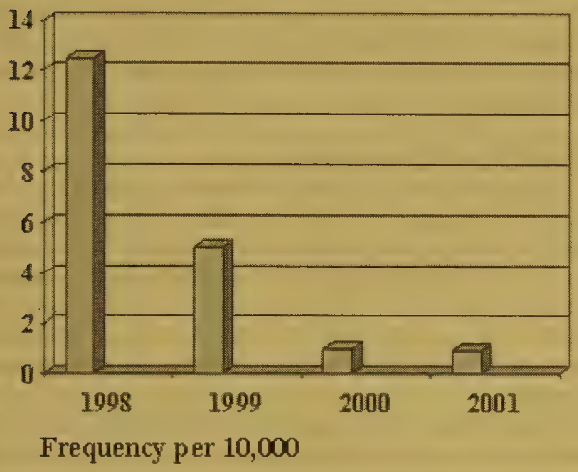

Figure 1. Banfield anesthesia mortality data.

pet's condition prior to anesthesia. Non-fatal adverse events must be considered critically important when determining quality anesthesia. Poor perfusion doesn't always result in patient death. For example, we want to avoid behavior changes or cortical blindness as a result of a hypoxic event that damages brain tissue during anesthesia. While these outcomes are not fatal, they are adverse anesthesia events, nonetheless. How many pets are no longer house broken as a result of brain damage from hypoxia? A great deal of data exists supports the fact that pets with behavior problems are more likely to be euthanized, thus supporting the need for high quality anesthesia.

Outcome analysis over the past years has noted many things:

- Anesthetic reactions are truly very rare.
- Lack of proper monitoring results in the appearance that patients are alive one minute and dead the next.
- Lack of understanding regarding proper drug usage and effects is common.
- Development of unique protocols (ie, bypassing standards) increases morbidity rates and mortality rates.

STANDARDS AND PROTOCOLS

Anesthesia is often considered to be synonymous with the anesthetic medications used. While the choice of anesthetic agents is important to case outcome, it is only a small portion of complete and successful anesthesia. It is important not to view anesthesia solely as selecting the right drug, but to look at how the pharmacology of the anesthetic agents affects patient perfusion while maintaining a "state of consciousness" that allows a procedure to be performed. To accomplish perfusion-maintenance, other factors besides pharmacology need to be considered. A total system for anesthesia is necessary which results in the development of standards and protocols.

When broadening the discussion of what is included in excellent anesthesia, equipment, patient health status and evaluation (including blood work), drugs and monitoring must all be considered. If an experienced doctor has the correct drug but the monitoring equipment is not functioning, an adverse anesthesia event or a fatal outcome can still result. Perfusion must be maintained during anesthesia, and as such, patients that are not monitored have higher morbidity and mortality rates.

Second, drug selection must be based on a working knowledge of drug interactions and their effects on perfusion. For example, if a patient is sedated with acepromazine, will that affect the safety margin of an alpha-2 agonist? Or, if ketamine is used for an aggressive cat, should atropine be given to prevent bradycardia? One of the many things that have been learned from outcome analysis is that all drugs are not compatible. Their physiological effects need to be understood well enough to be certain of compatibility. This complex matrix of premeds, induction agents, maintenance agents and emergency drugs makes well thought out protocols and standards essential.

Clearly, there is more than one way to practice anesthesia. Doctors in any practice can get similar results, provided that all components of the total anesthesia system (ie, equipment, monitoring, standard medications) are consistently utilized, and drug selection and dosages are compatible. Based upon the previously mentioned studies, and Banfield's ongoing outcome analysis, the veterinary profession can improve and obtain better outcomes. The first step in this process is to understand how drugs affect the autonomic nervous system and in turn affect patient perfusion.

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PERFUSION BASICS AND PROPER USE OF PREMEDICATION, TRANQUILIZATION, AND IMMOBILIZATION

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In accordance with broadening the practice of quality anesthesia, it is essential to evaluate the patient's health prior to administering premedication, or using tranquilization and/or immobilization techniques. Evaluating the perfusion of a pet before and during anesthesia is a key component to quality anesthesia management.

PERFUSION BASICS

Good perfusion can be defined as having adequate blood flow and volume to push red blood cells to the lungs where oxygen is picked up and then transported to the tissues to ensure that adequate oxygen delivery occurs. In order to maintain perfusion, blood volume, blood pressure, oncotic pressure, and cardiac output must be adequate.

Understanding cardiac output is critical to perfusion. Cardiac output (CO) is the product of heart rate (HR) and stroke volume (SV). Stroke volume depends on venous return (pre-load) and total peripheral resistance, mainly due to arteriole constriction (afterload) and contractility. Upon understanding this relationship, it is possible to understand how tachycardic patients with excessively high heart rates may have a stroke volume that becomes so small that no cardiac output occurs. For example, a cat with a heart rate of 250 beats per minute has literally no cardiac output. If the vagal system is blocked and the heart cannot slow itself, a patient may die from no cardiac output. It is important to remember that preload (venous return) and afterload (peripheral resistance) affect cardiac output as well. If a patient is hypertensive, the cardiac output is decreased because the heart is pumping against the smaller vessel size.

When considering perfusion, blood volume is also critical to maintaining blood flow. The protocols include IV fluids to make certain that the blood vessels are full. As blood vessels are also leaky, oncotic pressure affects perfusion. If the albumin and total protein levels are below normal, pulmonary edema may result during surgery. Patients that develop pulmonary edema during surgery may die several hours postoperatively. This is one of the reasons patients must be monitored for at least 2 hours postoperatively.

Evaluating the perfusion of a patient prior to anesthesia is just one component of the patient evaluation procedure. Within 48 hours prior to anesthetic induction, preanesthesia blood work, such as a complete blood count (CBC) with differential and internal organ function screen, should be performed. As always, it is important to review the patient's medical record completely, in addition to thoroughly evaluating the patient. Confirm that all participating team members are aware of every procedure being performed on the patient. After a complete physical exam, CBC with differential, and internal organ function screen, determine which premedication agents will be the most appropriate.

PREMEDICATION AGENTS

Premedications are used to calm the patient, reduce stress, and improve pet handling. Use of proper premedication agents will also decrease the required dose of induction and maintenance agents. In addition, premedications can improve induction and recovery quality, and some provide analgesia. Premedications are not used to immobilize in order to draw blood or place a catheter.

The premedication agents used will depend on the health status of each individual patient. Some of the more common agents available include acepromazine, butorphanol, diphenhydramine, diazepam, morphine, and a fentanyl patch.

Acepromazine

Acepromazine is a phenothiazine sedative/tranquilizer and an alpha-1 antagonist. As an alpha-1 antagonist, acepromazine results in vasodilatation of arterioles. This action is dose-dependent, so low doses result in slight vasodilatation and a large dose can result in hypovolemic shock. An important point to remember when using this agent is that anything Ace does, fluids can fix.

Butrophanol

Butorphanol is a mixed agonist/antagonist opioid. It can be used for pre-emptive pain management through effects on kappa and sigma receptors. This agent also has analgesic actions at the subcortical and spinal levels providing good visceral analgesia. Little respiratory depression is associated with butorphanol. Since butorphanol also acts as an antagonist to the mu receptors, it can also be used as a reversal agent for pure opioids whose analgesic action is mediated through mu receptors. It is important to remember that because butorphanol is a mixed agonist/antagonist, a ceiling is reached on its analgesic properties, meaning that higher doses do not proportionally equal more pain management. As higher doses are given, the likelihood of adverse effects developing tends to increase. Some of these adverse effects may include aggression, excitement and dysphoria. Therefore, to utilize butorphanol's analgesic properties, but avoid potential adverse effects, the maximum dose a patient should receive, regardless of size, is 5 mg.

Diphenhydramine

Diphenhydramine is an H1 antihistamine. Diphenhydramine can be used as a premed, rather than diazepam or acepromazine, when a patient has received, or is anticipated to receive, a transfusion to help prevent transfusion reactions. Diphenhydramine is preferentially used as the sedative, rather than

Ddazepam or acepromazine, when a patient is undergoing surgery for a mast cell tumor.

Diazepam is a benzodiazepine that produces sedation and skeletal muscle relaxation. It can also be of great benefit in a CNS protocol as it is an anticonvulsant, and will help to prevent seizures in higher risk patients such as the stabilized epileptic requiring a surgical procedure. Midazolam, a shorter acting, water-based benzodiazepine, is substituted for diazepam when it is unavailable. The dose for midazolam is 0.1 mg/lb given subcutaneously (SQ) or intramuscularly (IM).

Morphine

Morphine is a narcotic agent that has good analgesic properties. As a classic analgesic agent, it is an agonist of mu and kappa opioid receptors. Some respiratory depression is associated with morphine, and because it can cause vomiting, and causes histamine release if given intravenously, it should be given intramuscularly only. Morphine is used in standard Banfield Orthopedic and Ear protocols.

Fentanyl Patch

The fentanyl patch is a mu opiate agonist. It has good long-term analgesic properties of approximately 2 to 3 days. This agent can be used in the Orthopedic Protocol in conjunction with morphine. The goal is to use opioids for orthopedic surgery, then to transition the patient from opioids to nonsteroidal anti-inflammatory agents (NSAIAs) within 2 days, and maintain the patient on NSAIAs thereafter as needed. As a transdermal delivery system, it takes approximately 12 hours to take effect; and in some patients, it may take up to 24 hours. The patch is best applied to a shaved area.

TRANQUILIZATION/SEDATION

Determining whether or not a particular patient needs tranquilization/sedation will depend on the procedures being performed, as well as the temperament of the individual patient. Typically, a patient that has been tranquilized or sedated can still walk. Tranquilization/sedation can be used for procedures that may include blood collection, otoscopic exams, or to assist in restraint for nonpainful procedures, and to help decrease anxiety. Prior to administering a tranquilizer/sedative, a complete and deliberate physical examination should be performed. After tranquilization/sedation, it is important to continue monitoring the patient's TPR and pulse quality every 15 to 60 minutes depending on the patient. While the patient is tranquilized/sedated, it should be under visual observation at all times. The depth of tranquilization should be such that endotracheal tube placement is not possible. The use of a heart monitor (ECG) or pulse oximeter can be used at the doctor's discretion. In addition, an intravenous (IV) catheter may be placed. This procedure is recommended for pets over 5 years of age.

AIR TRAVEL

Traveling pets may require tranquilization/sedation. For air travel, Banfield will not prescribe acepromazine or other phenothiazine-type tranquilizers. Phenothiazine derivatives may block alpha-1 adrenergic receptors in the circulatory system, with subsequent vasodilation. This may create susceptibility to hypothermia and an inability to respond to changes in atmospheric pressure and temperature should a pet be in the cargo hold when something goes wrong. Instead of offering a phenothiazine derivative, diphenhydramine is prescribed. This agent will usually cause drowsiness, but does not cause circulatory side effects. Calculate the dose for each pet, 1 mg/lb by mouth, up to a maximum dose of 50 mg. Medication should be given approximately one hour prior to travel. This dose can be repeated every 6 to 8 hours as needed.

Prior to air travel, recommend to the client to acclimate the pet to the pet carrier for several days before the flight. This will decrease the stress that leads to barking, anxiety, and hyperexcitability. Putting a favorite blanket in the carrier and feeding the pet, or offering other treats while in the carrier, helps this process. Finally, recommend non-stop flights to minimize stress to the pet. Pets often get cold or hot while the plane is sitting on the ground.

Ground Travel

Inform clients that oral sedatives have variable effects on pets, and that they are more effective when administered before the pet becomes anxious or excited. Clients will need to closely monitor their pet's reaction to the sedative, and consult with the doctor for dosage adjustments. It is best to start with minimum doses. Recommend giving the agent prior to time of travel, in order to evaluate the pet's response. Also, recommend that the pet travel in a pet carrier whenever possible. Acclimate the pet to the carrier through favorite objects, treats, and feeding.

Oral agents recommended for ground travel include the following:

- Diphenhydramine 1.0 mg/lb PO (maximum dose 50 mg) q 6 to 8 hours
- Diazepam 0.1–0.2 mg/lb PO q 6 to 8 hours
- Acepromazine 0.25–1.0 mg/lb PO q 6 to 8 hours

Immobilization is typically used for procedures that can be completed in less than 10 minutes, are not painful, and do not require general anesthesia. When a patient is immobilized, it cannot walk, and is experiencing a nonsurgical plane of anesthesia. The patient can be aroused with minimal effort and maintains laryngeal and withdrawal reflexes. Immobilization techniques that usually do not require general anesthesia may include:

- Clipping matted hair
- Radiographs not requiring special positioning
- Mild ear cleaning

- Pedicure in aggressive patients
- To enable handling of fractious pets requiring general anesthesia

If a pet is immobilized and the doctor finds the procedure is more extensive than anticipated, general anesthesia may need to be performed. Preanesthesia blood work, IV catheter, and appropriate preanesthesia medications must be completed prior to induction of general anesthesia.

Prior to immobilization, certain requirements should be fulfilled. These include a complete and deliberate physical exam. Monitoring the depth of anesthesia is also important. The depth of anesthesia should be such that endotracheal tube placement is not possible. Continual monitoring and observation should be part of the protocol. Pulse oximetry can be used, and an IV catheter is required for propofol, and at the doctor's discretion for Telazol. The following agents can be used to immobilize patients:

- Telazol 0.5–2.0 mg/lb IM only (use low doses with debilitated patients). Maximum single dose is 100 mg
- Propofol 1.0–4.0 mg/lb IV

Immobilization Considerations in Brachycephalic Breeds

When working with brachycephalic breeds, the potential for apnea resulting in hypoxemia and/or hypercarbia during immobilization with propofol or Telazol is always a possibility, even in apparently healthy pets. Banfield recommends general anesthesia in all patients with the potential for upper airway or pulmonary compromise. These include the following:

- All brachycephalic breeds
- Those with excessive pharyngeal folds such as Shar peis
- Any pet with concern for abnormalities of the pharynx, trachea, larynx, and/or esophagus

This allows for immediate maintenance of a patient airway with an endotracheal tube and ventilation support with 100% oxygen. All general anesthesia prerequisites and monitoring procedures are necessary in these cases. The goal of this recommendation is prevention of unnecessary deaths during immobilization in a high-risk group of patients.

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SAFE AND EFFECTIVE ANESTHESIA INDUCTION AND MAINTENANCE

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General anesthesia in the pet practice plays a pivotal role in surgical procedures, radiographs requiring special positioning, invasive diagnostic procedures, and painful procedures. Also, general anesthesia is recommended over immobilization for all brachycephalic breeds.

ANESTHESIA INDUCTION

Induction methods should facilitate a smooth and calm transition to unconsciousness. However, induction is one of the most common times when adverse anesthesia events occur. In order to prevent adverse events, certain requirements should be fulfilled prior to induction. A complete and deliberate physical examination should be performed on the patient, including a thorough review of the patient's medical record.

Ensure that food and water have been withheld for 2 hours. No cases of aspiration have occurred in the practice by using this criterion. Longer periods without food and water (ie, 12 hours) can result in hypoglycemia, especially in pediatric patients. As part of the preanesthetic protocol, a complete blood count (CBC) with differential, and internal organ function screen should be completed within 48 hours prior to induction. An IV catheter should be placed, and an ECG and pulse oximeter can be used for monitoring. Ensure that premeds have had 30 minutes to take effect. If insufficient time is given, a much higher dose of induction agent will be required. Finally, if all preinduction requirements have been fulfilled, ensure that induction doses are administered carefully to effect. Mask or tank induction is not recommended because it is highly stressful causing catecholamine release.

INDUCTION AGENTS

Propofol

Propofol is an alkylphenol that is formulated as an emulsion. The emulsion components are a media that allows bacterial growth; as such, the product has limited shelf life after it has been opened. Propofol is a sedative hypnotic and generally has three main uses that include: use as an induction agent, immobilization/chemical restraint and anesthetic maintenance. As an induction agent, propofol can be used prior to an inhalant and can be given following premeds. As an immobilization/chemical restraint agent, propofol can be used for examinations and diagnostic procedures, for radiography and intradermal allergy testing. Finally, propofol can be used in anesthetic maintenance when intubation is not possible, in status epilepticus that is refractory to Diazepam and as a constant rate infusion at 0.1 to 0.25 mg/lb/minute. The duration of action is five to ten minutes with analgesia only occurring during unconsciousness. Side effects include apnea, cyanosis, and hypotension. Extravasation causes no tissue irritation.

Propofol is a media that allows for bacterial growth, and because it contains no preservatives, its use is limited to one working day. Whenever a bottle is opened, it should be thrown away at the end of the day. This product is not designed for refrigeration or freezing. Be sure to wipe the stopper with alcohol, following sterile technique, when drawing up a dose of this induction agent.

It is recommended to give one-quarter to one-third of the calculated dose as a bolus, assess the patient, and give the rest as needed to allow for intubation. The average dose of propofol following premedication is 1.0–3.0 mg/lb and 2.0–4.0 mg/lb if no premedication is administered. Cats often require closer to 3.0 mg/lb even with premedication.

Telazol (Zolazepam and Tiletamine)

Telazol is similar to diazepam and ketamine, but has greater synergism. Major uses include immobilization in routine cases, calming a fractious pet, intravenous (IV) induction when lipemia is present and induction for the Ear protocol if no other health problems are present. Zolazepam is a diazepinone minor tranquilizer. Telazol should not be the first choice with known cardiac disease, but is the safest drug in the Banfield pharmacy for a fractious pet in the absence of a complete medical history.

INTUBATION

Prior to intubation, it is always important to have all proper equipment ready, including various sizes of endotracheal (ET) tubes, topical Lidocaine (viscous), gauze and KY jelly. Use of a laryngoscope is always recommended. Choose an appropriately sized ET tube. Generally, the largest tube that will fit easily without trauma is recommended. Be sure that cuffs are tested for integrity before use. Measure the ET tube so that it will reach only to the thoracic inlet. Mark this location on the tube and tie gauze around it at this spot. If using a stylet, ensure that it does not protrude beyond the end of the ET tube. Lubricate the tube with KY jelly or its equivalent. While supporting the patient in sternal recumbency, gently pull the tongue out. For cats, it may be helpful to swab the vocal folds with Lidocaine, which helps to prevent laryngospasm. Laryngospasm is most likely to occur if forced intubation is attempted while the cat is too lightly anesthetized. It is important to remember that severe laryngospasm can kill. If a patient laryngospasms, place a large gauge needle into the trachea and administer pure oxygen until swelling decreases. Using a laryngoscope to visualize the laryngeal folds, place the ET tube into the trachea. Once the tube is in the trachea, secure it around the patient's upper nose or the back of the head, using the gauze strip. Listen for leaks before inflating the ET tube. It the tube is a tight fit, little to no cuff inflation is necessary. Using airway pressure as a guide, only inflate to prevent a leak to a pressure of approximately 20 cm water.

The cuff at the end of the ET tube is designed to close the air space between the outer walls of the tube and the inner walls of the trachea. This prevents the patient from breathing around the tube, or, receiving an inadequate or inappropriate amount of oxygen and anesthesia. Before using the ET tube, be sure to check the cuff for leaks. This can be accomplished by gently inflating the cuff with a syringe of air. (Over-inflation will destroy the cuff.) Watch the balloon inflate. Gently squeeze the balloon to determine if there are any leaks. Once it has been confirmed that there are no leaks, deflate the cuff by reattaching the syringe and withdrawing the air. The cuff should be deflated before intubation.

ANESTHESIA MAINTENANCE AND MONITORING

Sevoflurane

Sevoflurane is a newer gas anesthetic maintenance agent. Use of this agent requires a specific sevoflurane vaporizer. Sevoflurane can be used in circle or non-rebreating circuits. It has similar properties to Isoflurane with some differences: .

- It has a lower solubility than Isoflurane, which allows for rapid changes in the depth of anesthesia. Due to this potential of rapid change in depth, it allows for more precise control, but also requires closer monitoring because it is easier to have a patient extremely deep within a few minutes.
- At maintenance levels, the vaporizer will normally be set to between two and three percent. The vaporizer setting and end-tidal sevoflurane concentration are slightly different. Patients that are ill or compromised will often need a vaporizer setting of less than two percent.

Return to full consciousness is usually rapid. This is especially important in brachycephalic breeds where airway compromise is prevalent. Premedications tend to decrease excitement during recovery.

Oxygen Flow Rates During Anesthesia

When using the Unilimb (Universal F Circuit) anesthesia tubing (a re-breathing system), current anesthesia protocols call for oxygen flow rates of three liters/minute during the first three minutes of anesthesia with the sevoflurane level at 3% when pets are induced with propofol. This results in a smooth transition from induction to maintenance anesthesia. This is not done with a Telazol induction. Following the transition phase, oxygen flow rates are decreased to 1.0–1.5 liters/minute. In the majority of patients, higher oxygen flow rates are not necessary to maintain oxygen saturation of greater than 94 percent. Higher oxygen flow rates vaporize sevoflurane faster, thus increasing the cost of anesthesia.

Assisted Ventilation

When assisted ventilation is necessary, it is important to deliver the correct inspiratory pressure to avoid adverse pulmonary function or complications.

- 12 to 15 cm water for small pets and pets with chronic pulmonary disease,
- 20 cm water for medium to large pets,
- 25 cm water may be required for giant pets.

Ventilation should be delivered in a manner similar to normal respiration, avoid holding inspiratory pressure. The manometer should return to zero between breaths when no pressure is on the bag. The pressure relief "pop-off" valve should be open when not assisting ventilation and should only be closed enough to reach desired positive pressure during assisted ventilation.

Monitoring

The importance of monitoring patients during anesthesia is to evaluate tissue perfusion. Anesthetics depress autonomic nervous system function, which is what maintains perfusion. Monitor multiple systems for trends. The primary cause for crisis during or after anesthesia is the failure to notice a problem when it occurs. The three goals of monitoring are to anticipate, recognize and correct complications. The patient should be continuously monitored until a sternal position can be maintained.

Anesthetic depth and patient condition are dose dependent. As the anesthetic dose is increased, depth is enhanced and anesthetic safety margins decrease. Anesthetic depth is determined by skeletal muscle tone, selected reflexes (including jaw tone and withdrawal) and corneal position. Direct response to surgical stimulation is the most reliable indicator of determining depth of anesthesia. If uncertain about a patient's anesthetic depth, assume that he/she is too deep. If monitoring the end tidal CO_2 (ET CO_2) patients should be maintained between 35 and 50 mm Hg.

Hypothermia (body temp below 98°F, 37°C) is common after 30 minutes of surgery. Hypothermia enhances depression, prolongs recovery and increases stress. Signs of hypothermia include cyanosis, arrhythmias, cool extremities, decreased respiratory rate and shivering. For every degree body temperature falls below 100°F, the anesthesia requirements decrease by approximately 5%.

It is best to prevent heat loss with pads, warm IV fluids, using warm surgical scrub and minimal amount of alcohol during the surgical prep. These methods will not decrease body temperature, but will slow heat loss. Warming patients can be accomplished by two methods that include surrounding the patient with warm air and warming the inspired air. When surrounding the patient with warm air, use a trash bag with a hole cut in the bottom of the bag for the head to protrude. In the open end of the bag, circulate warm air with a hair dryer. This provides warm air in contact with enough surface area to warm the patient. When warming the inspired air, use a warm water trap added to the anesthesia machine, or by shining a light bulb on the soda lime canister. Care must be taken to prevent the temperature of the soda lime from exceeding 100°F; place thermometer strips on the canister in various locations to monitor canister temperature.

Recovery

Along with induction, recovery is another common time for adverse anesthetic reactions to occur. It is important to continue monitoring TPR and pulse quality until the patient is able to sit sternally and is fully alert. Maintain a pulse oximeter on the patient until he/she is fully awake and ensure that monitoring of patient is documented in the medical record. Deflate the cuff on the ET tube at the first sign of increased consciousness. Signs of increased consciousness include increasing jaw tension, and increased swallowing. As the patient begins to swallow or move the jaw, remove the ET tube. Once the patient is sternal and normothermic, the Pet may be moved to a kennel. Fractious or dysphoric dogs can be given 0.025 mg/lb Acepromazine IV slowly (maximum dose is 1.5 mg) to effect for rough recovery. This is given only during recovery. Check for hypothermia and hypoglycemia if recovery appears to be slower than normal. Correct these conditions if present.

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PHEROMONES: RECENT ADVANCES AND CLINICAL CASES

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EVALUATION OF THE EFFICACY OF A SYNTHETIC PHEROMONE ANALOGUE IN THE TREATMENT OF STORM PHOBIA IN DOGS: A PILOT STUDY

Subjects and Methods

Twelve storm-phobic dogs, two neutered males and ten neutered females, were treated with a combination of dog-appeasing pheromone (DAP) and behavior modification in an open, pilot study of this treatment protocol. Patients were recruited from dogs owned by the faculty, staff and students of the University of Georgia College of Veterinary Medicine. To be included in the study, dogs had to be at least 6 months of age, not have any history of aggression, health problems or other significant behavior problems. They had to have exhibited at least one of the following behaviors on three different occasions during storms: elimination, excess salivation, excess vocalization, destructiveness, hiding, pacing, panting, self-trauma, staying near the owner, or trembling. A Storm Phobia Assessment questionnaire (SPA) that has been used in previous research on the treatment of storm phobia[1] was also completed for each patient. Dogs with a score of 10 or less were not included, as dogs with this score were considered to have very mild storm phobia that owners are not likely to present as a problem. Dogs with a score greater than 30 were also not included, as this constitutes dogs with a very severe problem that are likely to require medication in addition to more conservative treatment. Dogs with scores from 11 to 30 were included.

Treatment consisted of providing DAP as a continuous diffuser in the location where the dog spent most of its time and desensitization and counter-conditioning with storm CDs for 10 to 15 minutes a minimum of 3 days a week. Owners were also instructed to neither punish nor comfort their dog if it acted afraid during storms.

All participants were provided with diaries in which to record whether or not there were any storms that day, the specific characteristics of the storm (eg, thunder, lightning, rain, strong winds), the dog's response to the storm, and whether or not they checked the diffuser to confirm that it still had liquid in it and was plugged in. Dogs were treated for a minimum of four storms. At an exit visit that occurred after a minimum of four storms, a second SPA questionnaire was completed by the owner. In addition, owners completed global assessment forms. Dogs experienced 4 to 12 weather events during the course of treatment.

RESULTS

Nine dogs showed decreased SPA scores ranging from 5% to 75%. Two dogs, one female and one male, had increased SPA scores, while one dog showed no change. The Wilcoxon Signed Ranks Test comparing pre- and post-treatment scores was significant ($P = 0.018$). The mean percent decrease in SPA score was 25%.

The two dogs that had an increased SPA score exhibited increases of 16% and 18%. The two dogs with the largest decrease in score exhibited decreases of 75% and 69%. In their global assessment, owners had a choice of Worse, Unchanged, Somewhat Better, Substantially Better but Not Resolved or Resolved. No owners rated their dogs as Worse or Resolved. Five owners rated their dogs as Somewhat Better, four as Substantially Better but Not Resolved, while three owners rated their dogs as Unchanged. Thus, 9 out of 12, or 75% of the owners believed that their dogs had shown some degree of a positive response during treatment. There was no relationship between the number of weather events experienced during treatment and improvement. There was not a significant relationship between beginning SPA score and change in SPA score. The three dogs with the greatest decrease in their SPA scores had pre-treatment SPA scores of 23, 24, and 29. The three dogs that had no change or an increase in their SPA had pre-treatment SPA scores of 17, 21, and 25

CONCLUSION

DAP may facilitate improvement in symptoms of storm phobia. Since this was a pilot study and the dogs also received some behavior modification, further research is needed to confirm this.

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PRACTICAL APPROACH TO THE TREATMENT OF SEPARATION ANXIETY IN DOGS

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Because domestic dogs usually consider the human family to be their social group, they become bonded to family members. When separated from family members, dogs may experience distress and engage in problem behaviors related to the anxiety of separation. These behaviors include destruction, vocalization, elimination of urine and/or stool, anorexia, drooling, attempts at escape, and/or behavioral depression. Treatment protocols include independence training, habituation, counter-conditioning and desensitization to owner departure and absence, pheromones. and pharmacological intervention.

HISTORY TAKING

Separation anxiety seems to be quite prevalent in the companion dog population. Dogs that are adopted as adults from humane shelters appear to be over-represented in case loads of dogs diagnosed with separation anxiety. The problem behavior(s) cited are destruction, vocalization, and/or elimination in the house while the owners are gone.

The dog may engage in only one of these behaviors or all three or other problem behaviors may be present. Geriatric dogs are more commonly seen for the behavioral complaint of separation-related anxiety when compared with younger dogs.

Diagnosis of separation anxiety should not be made solely on the basis of destruction or vocalization when the dog is left alone; in many cases signs of increased attachment to the owner and distress as they get ready to depart is noted. Dogs with separation-related anxiety often follow their owners while they get ready to leave or keep them within their field of vision. Dogs may exhibit anxiety by whining, panting or pacing while others become immobile, as the owner gets ready to depart. Most dogs engage in the separation-related behaviors within 30 minutes of owner departure. Self-mutilation, excessive licking, and vomiting or diarrhea can also occur as symptoms of separation distress. While most of the problem behavior occurs shortly after owner departure, some dogs may cycle through periods of re-arousal perhaps brought on by outside stimulus.

An additional component in the history of separation anxiety dogs is their excitement when their owner returns. Their greeting behavior is often exuberant and prolonged. In addition, dogs with separation anxiety are at risk for noise phobias and dogs with noise phobias appear to be at risk for separation anxiety.

DIAGNOSIS

Before establishing a diagnosis of separation anxiety, other causes of house soiling, destruction, and vocalization must be ruled out. Differential diagnoses for dogs that eliminate when left alone include medical causes of house soiling, inadequate house-training techniques, marking, and prolonged periods without access to appropriate elimination locations. When dogs are destructive or barking, alternate explanations including young, energetic dogs with limited exercise or play, external stimuli, and territorial displays should be explored. Destruction may be a component in noise phobias such as thunderstorm phobias. Geriatric dogs may be experiencing changes in cognition and should show other signs of cognitive decline such as wandering, loss of house training, disturbances in sleep/wake cycles, and other symptoms that have been associated with Cognitive Dysfunction Syndrome. Some dogs may be distressed when the owner is gone due to fears, phobias or anxieties about events that occur in the owner's absence such as storms or other loud noises. If none of these apply, then a diagnosis of separation-related anxiety is appropriate. If the history is not clear, then owner journals, audio and/or video tapings, and appropriate medical testing may be helpful in establishing a diagnosis. In some situations, more than one dog is showing anxiety and distress and all patients must be treated.

TREATMENT

Standard behavior modification treatment plans generally have the following components:

Owner Education

Owners need to be counseled that the behavior is anxiety based, not spiteful.

Restructuring the Pet–Owner Relationship

Owners should be given tools to make the dog less attached and their interactions with their pet more focused and structured. Ignoring attention-seeking behaviors, teaching sit/stay, decreasing following behaviors and earning attention by performing a task first are commonly recommended. A predictable routine for exercise, play and attention should be established and followed. Teaching the dog to settle and relax in a set location or on a bed or mat can be useful to teach the dog how to be calm on cue. Once learned, this can be helpful to calm the dog before owner departure.

Departures and Returning: Habituation to the Pre-departure Cues, and Changing the Leaving and Return Routine

Animals quickly learn to associate various departure cues (getting keys, briefcase, lunch, etc.) with the owner leaving and may become anxious when these are performed. The goal is to reduce the predictive value and thus anxiety producing quality of the steps in the owner's departure routine. In order to uncouple these cues from actual departures, the owner is asked to perform them without leaving. For example, the owners might pick up their keys or purse, put on a coat, or open and shut the door without actually departing. This can be repeated two to four times a day but it is essential that the dog be calm between presentations. The process is successful if the dog no longer responds to the presentation of the identified cues with anxiety. Owners are also counseled to ignore the dog for 15 to 30 minutes prior to departure and upon return to keep these times neutral and calm.

Counter Conditioning to Departure

Teaching the dog to engage in an alternate activity when the owner approaches the door and/or departs may help some dogs cope more easily with owner departure. This can be a simple "sit/stay" or the use of a food stuffed toy prior to departure. The dog can also be asked to settle in its previously learned safe location.

Graduated Planned Departures

The goal is to replicate real departures, using a new signal to facilitate the dog learning that departures need not produce anxiety. Because these are difficult to properly execute, a more detailed explanation follows below. These are generally not begun until the dog can settle and relax on cue and no longer responds to departure cues with distress.

Actual Departures During Treatment

Most owners must still continue to work while treating the pet. Alternate solutions may be useful until treatment begins to change behaviors. These can include doggy daycare situations, pet sitters, and boarding. Confinement may be problematic for some pets and increase their anxiety and subsequent damage to themselves or owner property.

GRADUATED PLANNED DEPARTURES

Graduated planned departures are best started after the dog has been habituated to pre-departure cues. Using short departures, the goal is to desensitize the dog to the owner leaving and being gone. These departures are as much like real departures as possible with two exceptions. First, the departures are going to initially be **very** short. Second, as the owner departs they leave a new and consistent cue or signal for the dog. The goal is for the dog to associate the owner departure, the new signal and good behavior with each other as the dog learns how to left alone. Then the initial departure will be very short, 1 to 5 minutes or less so that the dog does not engage in any separation related behaviors. ***But, they will leave the dog a new cue or signal like the radio or television or air freshener to aid the dog in distinguishing this departure from a real or work departure.*** The goal is for the dog to learn "the owner is only gone for a short time, they are coming right back and I can be good." The length of the departure is **slowly increased** at 3- to 5-minute intervals with short departures interspersed with longer ones. The increase must be irregular, not a progression. The new cue is only used on a planned departure, *never* when the owner must be gone for long periods of time such as going to work. If the dog is destructive or engaged in any separation-related behaviors during a planned departure, then the owner was gone too long and the next departure should be shorter. For dogs that vocalize on owner departure, an audio tape should be set to monitor the pet's behavior. Owners must keep initial departures short enough so as not to elicit separation distress. When desensitization is done improperly, sensitization can occur and the problem behavior worsens.

Once a dog can be left on a planned departure for 2 hours, they can usually be left all day. The cue or signal can be gradually phased out, or can be used for as long as the owner feels it is necessary. Most importantly, the owner cannot quickly go from a 20-minute planned departure to a 3-hour one. This can elicit separation-related distress and may render the cue useless. During training, owners should be encouraged to keep journals to assess progress and treatment success. In many cases, once the dog can be left alone on a planned training departure for 2 hours, the dog can stay alone all day.

The use of barriers and crates must be evaluated in each case. For many dogs these actually heighten, rather than lessen anxiety. If the owner is willing to leave the dog out of the crate or not barricaded in a room during training departures this can be useful to help the dog distinguish these departures from routine work related departures.

Punishment must be avoided even if the pet has been destructive or eliminated while the owner was gone. Punishment increases anxiety and is not productive or helpful in resolving the problem behaviors.

DRUG AND PHEROMONE THERAPY

Many drugs have been used in the past for the treatment of separation anxiety in dogs. These include: tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), buspirone, and benzodiazepines. Prior to medications a physical examination and a minimum database of a biochemical screen, complete blood count (CBC), and urinalysis should be performed. Results with drug therapy may not be seen for 14 to 30 days, the owner must be committed to continue usage. Two drugs are presently formulated and licensed for the treatment of separation anxiety in dogs; clomipramine hydrochloride (Clomicalm®)[a] and fluoxetine (Reconcile®)[b] are now labeled to aid in treatment of separation anxiety. Tricyclic antidepressants (TCA) as a class of drugs primarily affect serotonin, norepinephrine, acetylcholine, and histamine. TCAs are contraindicated in hyperthyroidism; seizure disorders; in animals on thyroid medication, amitraz, or selegiline; or animals experiencing problems with urinary retention or urine flow. Common side effects with TCAs include urinary retention, constipation, tachycardia, dry mouth, hypotension, and mydriasis. Clomipramine is dosed at 2 to 4 mg/kg per day either as one dose or divided twice daily. The most common adverse reactions are vomiting, diarrhea and lethargy. Caution is advised in using clomipramine with other CNS active drugs including general anesthetics and neuroleptics, anticholinergic and sympathomimetic drugs. In the placebo-blinded drug approval study, the medication was used in conjunction with behavior therapy and withdrawn after 2 months. After week one, 47% of the dogs receiving clomipramine and behavior modification showed improvement compared with 29% of the dogs receiving behavior modification alone. In another placebo study by Podberscek et al on treatment for separation anxiety, it was found that the clomipramine patients either at a low dose (0.5–1.0 mg/kg bid) or a high dose (1.0–2.0 mg/kg twice daily) showed no greater improvement than those on placebo. However, behavioral therapy on its own was highly effective.

In a large multicentered double-blind, placebo-controlled study, fluoxetine was dosed at 1 to 2 mg/kg once daily. Dogs in both groups received behavior modification. Seventy-three percent of dogs treated with medication and behavior modification showed improvement in overall severity scores compared with 51% of behavior modification alone dogs at the study conclusion after 8 weeks. Forty-two percent of treated dogs showed improvement within the first week. In this study, the frequency of adverse events was generally similar for fluoxetine- and placebo-treated dogs. The most common adverse events reported following fluoxetine treatment were lethargy and vomiting. Seizures occurred in three fluoxetine-treated and one placebo-treated dog; therefore, fluoxetine is not recommended in dogs known to suffer from a seizure disorder. Full details of the study are recently published. Fluoxetine should not be used concurrently with monoamine oxidase inhibitors (selegiline and amitraz).

Fluoxetine and clomipramine should not be used concurrently due to the risk of producing serotonin syndrome. When either is used in a treatment program, the medication must be given daily and may take 2 to 4 weeks to see some effect. Patients may need several months of treatment for sustained improvement to be noted. In some cases withdrawal of medication may result in the return of symptoms.

Benzodiazepines have often been suggested for immediate relief or short term control. Benzodiazepines such as alprazolam (0.02 to 0.1 mg/kg orally) can be dispensed on an as-needed basis shortly before departures. Benzodiazepines may inhibit learning, usually require frequent dosing and may cause dependence and a rebound anxiety when discontinued.

DAP® (Dog Appeasing Pheromone)[c] may be useful in reducing anxiety associated with owner departure in some dogs. DAP is available as a diffuser that plugs into the wall and remains active for 30 days. One study comparing the efficacy of DAP versus clomipramine for the treatment of separation distress in dogs found to be them to be approximately equal with respect to owner global assessment scores and there were no significant differences between the two groups in individual signs.

PROGNOSIS

Takeuchi et al evaluated treatment outcome in dogs with separation anxiety and owner compliance and perception of effectiveness of treatment recommendations. Fifty-two dogs were evaluated and the researchers found that 32 were improved and 20 were the same, worse, or had been euthanized or given away. Significantly fewer dogs whose owners were given more than five instructions improved or were cured when compared with those given fewer instructions. This may reflect the difficulty of compliance, time commitment, or lack of understanding of the treatments prescribed. Twenty-seven were treated with medication (often amitryptyline probably because cases were from 1993-1997) and 15 improved. Owners complied with instructions that required little time such as chew toys at departure, increasing pet exercise, and omitting punishment. Often owners were not willing to uncouple departure cues or desensitize to impending departures.

WHY TREAMENT RESULTS VARY AND MAY FAIL

- Drug therapy alone is rarely curative for most behavioral disorders. Realistically, drug therapy can be expected to decrease the anxiety associated with owner departure. However, the drug alone will not change behavior and will not “teach” the pet new behaviors. While some behavior may be decreased, some will persist and even at high levels.
- If the pet is not taught how to remain home alone, and anxiety-producing cues are not habituated to, very little improvement might occur. In fact, some dogs may become worse.
- Concurrent additional anxieties (storm phobias, noise phobias, inter dog aggression issues) that are not addressed may limit treatment success
- Owner expectation of a “quick” cure. Owners are used to pharmacological treatments from their veterinarian resulting in a fairly rapid response from their pet. This usually does not occur with behavioral drugs.
- The ongoing destruction, vocalization, and elimination continue to strain the human–animal bond

IMPROVING PROGNOSIS

Because behavior disorders take time to diagnose and treat, veterinarians need to set aside a separate appointment to discuss the problems and completely explain the treatment plan. Emphasis on habituation, changing the pet–owner interactions and changing the leaving and return are important and relatively easy for owners to implement. Because it is easy to make the dog worse through improperly applied techniques, it is extremely important that the practice set aside time for regular follow up with owners of dogs with separation anxiety. Continued information and feed back is needed to see if the owners are properly administering the behavioral treatment plan. Owner journals can help assess progress and are often essential to monitor progress. Finally, medication can take 2 to 4 weeks to have an effect on behavior and must be given daily, not on an as needed basis. Therefore, it is crucial that the veterinary staff supports the owner's work with behavior modification. When no response is noted, the diagnosis should be re-evaluated and other concurrent behavioral problems also addressed.

An initial response to therapy is usually seen in 2 to 6 weeks depending on the number of trial departures that the owner is able to do and how the pet responds to the other components of the treatment plan. Total treatment time may be several months, for some dogs 6 months or more. Once the dog can reliably be home for 6 to 8 hours in all situations without the previous separation-related behaviors occurring, medication can be decreased. The dosage should be decreased at 25% per week while watching for reoccurrence of target behaviors. This is absolutely essential. If the dog begins to show any anxiety, either stay at that level for a longer period of time or increase back to the previous level. Early withdrawal of medication may result in the return of the separation anxiety and possibly are higher levels that before.

FOOTNOTES

[a] Novaris Animal Health, Greensboro, NC

[b] Lilly, Indianapolis, IN

[c] CEVA Sante Animale/VPL in US

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SEPARATION ANXIETY IN DOGS, PART 1: DIAGNOSIS AND CLINICAL PRESENTATION– AN EVIDENCE-BASED APPROACH

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The sensitive period in which puppies develop social attachments to the living environment (people and other pets) and to nonliving parts of the environment (localization or site attachment) is between 3 and 12 weeks of age. The process of becoming more fearful may begin at 6 to 8 weeks of age, but generally social attraction outweighs wariness until an upper limit of about 12 weeks. Socialization to a new species may be possible after this age but may take months of exclusive contact. Of course this upper limit may vary between breeds and individuals and without continued socialization further regression might occur.[1,2]

The mother or primary care giver provides a secure base from which the young begin to explore their world and gain confidence. Puppies become distressed if separated from their mother at three weeks, which rises to a peak at about 6 to 7 weeks and then declines at 12 to 14 weeks. However, puppies that are first separated from their mother at 9 to 12 weeks may exhibit more stress than puppies that have had previous separation. Separation vocalization and separation destruction are intended to restore contact with mother, social group, or care givers.[1-4]

Domestication and selective breeding may lead to increasingly affectionate, socially dependent and infantilized dogs which may inadvertently lead to excessive owner attachment and intolerance to being left alone.[1,5] Puppies that come to expect excessive social interactions following adoption at around 3 months may be unable to handle subsequent decrease in social interaction, and may become sensitized to departures.[6,7] Therefore, gradually introducing puppies to separation and enforcing time away from puppies may help them better cope with spending time alone.[1,6-8] In addition, puppies vaccinated prior to 8 to 9 weeks were at lower risk for separation anxiety.[1] On the other hand, providing extensive social experience between 5 and 10 months may be associated with an absence of separation anxiety.[6]

Mothers who are anxious or ambivalent may lead to more clingy, over-dependent infants who are distressed by separation.[1] In addition, dogs that were ill as puppies have also been shown to develop more separation related barking.[1] While these early experiences may influence the development of separation anxiety, it is most likely that genetics plays a primary role in the disorder.[1,4,5,6,8] Genetic variability may vary between individuals or there may be breed prevalences.[9] When separation distress reactions persist beyond the puppy stage they are maladaptive and may be indicative of a either dysfunctional attachment or perhaps even a pathological state.[5,10-12]

Since drug and pheromone therapy have been shown to be effective in reducing attachment behaviors and improving separation anxiety (in conjunction with behavior modification), compared with behavior modification alone, this may further indicate that neurochemical factors contribute to separation anxiety.[13-19] In fact, although concurrent behavior management is a necessary part of an effective treatment program, in one study fluoxetine alone had some beneficial effect on reducing anxiety even without the addition of behavior therapy.[19] In another study, clomipramine treated dogs had less solicitous behaviors and were overall more calm.[20] In another study dogs that were timid fearful and restless when removed from their social environment, the dogs were less socially solicitous and could be better trained to sit when treated with low dose morphine (0.25 mg/kg) and morphine treated animals were less socially solicitous.[21] When treated with naloxone the problem was aggravated and dogs were more solicitous.[21] In another recent publication, prolactin levels were found to be significantly higher in dogs under chronic stress, but significantly lower with fear and mild phobias, which indicates that anxiety disorders may differ in neurochemistry and in the drugs with which they might be treated.[22]

Separation anxiety may also arise as a secondary or acquired condition or have a learned component. For example, separation anxiety may arise when a dog is suddenly separated from its owners following a period of prolonged, constant or exclusive contact or a sudden change in routine.[1,7] These dogs may develop an overly intense attachment and may then be unable to with separation. In addition, separation anxiety may develop in individuals that have other anxiety disorders, such as noise and storm phobias and separation anxiety.[23-25] These dogs may become dependent on the owners to alleviate their anxiety and in turn, the owners' responses, whether reinforcement or punishment may further intensify the behavior. Yet, some of these dogs are well adapted to remaining alone at certain times or in certain environments, eg, cars.[3,5,12] This may be due to the absence of specific departure cues that lead to an anxiety or a difference in the owner's response to the dogs at certain times or in certain places. In the French literature, separation distress that occurs in the adult dog may be considered a depressive disorder, in which the destructiveness, vocalization and other autonomic signs of separation anxiety, which may even be displayed. Pre-sleep anxiety, sudden awakening, elimination during sleep, altered appetite and depression are also frequent signs.[11]

CASE DISTRIBUTION

Separation anxiety represents from as low as 9% to as high as 35% of cases referred to veterinary behaviorists.[3,7,23,31] However, in senior dogs, 29% to 50% of referred cases may be due to separation related distress.[28-30] This may be due to concurrent underlying medical problems, reduced cognitive capacity or the fact that older pets are less adaptable to change and stress especially a change in routine or death of another dog or family member. Therefore while a diagnostic evaluation including physical examination and laboratory screening is an essential step in any veterinary diagnosis, and prior to any drug use, it is of particular importance in the adult or senior pet that develops separation anxiety.

However, the prevalence at these referral practices does not necessarily represent the prevalence amongst dog owners in general. In one survey, 14% of dogs receiving regular veterinary care reported signs associated with separation anxiety,[5] while in a study of veterinary surgeons in the UK, it was estimated that about 15% of dogs have separation anxiety.[31] In a survey commissioned by Lilly (internal data) the prevalence was found to be as high as 17% of all dogs, yet only about 10% of these have been identified. This reporting rate is similar to a study in the UK in which 29% of 94 pet owners reported separation anxiety, but only 6 of the owners had sought assistance.[6]

FACTORS ASSOCIATED WITH SEPARATION ANXIETY

Source

A number of studies have indicated that shelter dogs are overrepresented in cases of separation anxiety.[14,22,23,32] However, other studies have found no correlation.[6,27] In fact in one study 33% of dogs were from shelters,[33] and in an Australian study in which 68% had been obtained from breeders or friends, the authors speculated that the lower proportion of shelter dogs may have been due to increased shelter dog screening.[34] Therefore, it appears that for the most part that when shelter dogs are overrepresented, it is because they already had separation anxiety at the time of relinquishment.[32,35-37] In fact, screening and assessment of shelter dogs, and provision of appropriate advice to those who adopt these pets can effectively reduce separation anxiety.[32,34-36] On other hand it is also interesting to note that dogs that experience the loss of an attachment figure may develop more insecure attachments,[1] and that dogs that dogs that had been previously abandoned were more anxious and had less secure bonds with their owners than puppies that had been with their owners since puppyhood.[37,38]

Sex, Breed, and Household Factors

If one were to examine individual studies then breed and sex trends are evident. However, by comparing numerous studies using a variety of methodologies and populations, there appears to be no breed or sex correlation. In some studies mixed breeds were more prevalent,[3,23,25] while in other studies there was no difference between pure and mixed breed,[6] or purebreds were more commonly represented.[33,34] Some studies have indicated that males are more commonly affected,[3,6,13,20,39] and one study indicated that intact males and females were one third less likely to display separation anxiety.[23] However, in one European study, there was no difference in sex distribution although there was a higher percentage of intact males and females (but neutering is far less common in some European communities), although there was no difference in sex distribution.[16] By contrast fears and anxiety are reported to be higher in females than males.[9] However, a large number of studies have found no correlation between sex and neuter status.[6,20,26,27,34] The presence of another pet has been consistently shown not to be protective.[23,27,34,40] Another study looked at age of adoption and found that puppies adopted prior to 12 weeks were at no greater risk.[23] Two studies specifically examined family makeup and conclusions were contradictory. In one study a single owner was 2.5 times more likely to have a separation anxiety problem than multiple owner homes.[23] However, in another couples with children were overrepresented.[34] Most other studies did not evaluate family makeup.[13,15,16,19,20]

The Relationship Between Training and Separation Anxiety

Although one study found no association between spoiling, obedience training and behavior problems.[31] A number of more recent studies have found a trend toward less separation anxiety and less behavior problems in dogs that have had obedience training.[14,40,42] In fact, dogs that have obedience training, have been trained with positive reinforcement, or have been to agility classes are less likely to have behavior problems, while those dogs trained with punishers had lower obedience scores and a higher level of training problems.[43,44]

DIAGNOSIS AND CLINICAL SIGNS

The most common signs of separation anxiety are vocalization, destructiveness, and, to a lesser extent, house soiling during the owner's absence.[3,5,7,11,23,23,40] Since the anxiety is due to the dog's anxiety is due to its inability to gain access to the owners, the behavior is not likely to be seen when the owners are at home and the dog has access to the owners. When owners are at home dogs with separation anxiety also commonly exhibit extreme following, continuously seeking contact, departure cue anxiety, rarely spending time outdoors alone, and excessive greeting.[3,7,23] When the owners depart, destructive activity is often focused on doors, confinement area exits, or owner possessions, such as clothes and furniture.[3,5,7,23] Many of the signs are directly related to the autonomic arousal that accompanies anxiety. Concurrent signs of depression, anorexia during departure (which resumes when the owner is home), vomiting and diarrhea, and hypersalivation are highly supportive.[5,7,23,39] Other concurrent signs may include increased motor activity,[3,5,40] excess licking or grooming,[15,16] restlessness,[15] shivering and shaking,[16] stereotypic or repetitive behaviors such as acral lick dermatitis, ritualized circling and pacing,[5,13,40,45] and occasional reports of aggression as the owners prepare to depart.[3,7,46] Most signs tend to arise within the first 30 minutes of departure and many appear prior to, during or immediately following the owner's departure.[3,7,39,40] Signs may decrease over time or have a cyclical nature to their recurrence ranging from 25 to 28 minutes[40] to 40 to 60 minutes.[39] In addition, external stimuli also lead to rearousal.[40] The distribution of signs as collected from the various published studies are listed in Table 1.

Prognosis

In a study of 52 dogs that were followed up 6 to 64 months after their visit, 32 dogs (62%) improved; 24 (46%) improved and 8 (16%) resolved. Twenty of the dogs were the same, worse, or had been euthanized or given away (7 same, 3 worse, 5 euthanized and 4 given away).[39] In this study, 27 dogs were treated with amitriptyline and 56% improved. However, recent studies combining clomipramine, fluoxetine or DAP with behavior modification achieved much higher results (see Part 2 of this article).

Significantly fewer dogs were improved or cured when owners were given more than five instructions. Owners complied with instructions that required little time, such as chew toys at departure, but were less willing to institute more difficult tasks such as uncoupling departure cues or desensitizing the pet to departures.

While a comprehensive behavior consult with case-specific instructions that are tailored to the owner's needs might be most successful in an owner who is willing and compliant,[20,47] studies have shown that success can generally be achieved by combining a simplified behavior modification program with a drug or pheromone that reduces underlying anxiety.[13-18,48]

Table 1. Distribution of Reported Signs

- **Destructive:** 90%[40], 84%[7], 83%[19], 80%[3,15], 76%[13], 72%[16], 71%[23], 62%[17]
- **Vocal:** 96%[40], 90%[3], 73%[13], 67%[16], 61%[23], 48%[17], 41%[7]
- **Eliminate:** 55%[3], 53%[16,17], 28%[23], 18%[7], 5%[40]
- **Urinate:** 42%[19], 36%[13], 34%[15]
- **Defecate:** 37%[13], 32%[19], 27%[15]
- **Salivate:** 43%[19], 35%[15], 17.5%[16]
- **Feeding:** 46%[16]
- **Licking:** 40%[16]
- **Sleep:** 23%[16]
- **Vomiting and diarrhea:** 19%[23]
- **Stereotypic or displacement;** 10%[40]

References are available from the author upon request.

SEPARATION ANXIETY IN DOGS, PART 2: THERAPEUTIC OPTIONS – AN EVIDENCE-BASED APPROACH

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A behavior management plan is required to help the pet reduce its overdependence on the owner and to train and shape behavior to achieve a calm and relaxed state even when the owner is not present. However, as discussed in Part 1 of this two-part article, because the attachment is generally dysfunctional, the anxiety can be quite intense and there may be other concurrent fears and anxieties co-existing. Therefore, when behavior modification is combined with drug or pheromone therapy a faster and greater improvement has been shown to be achieved.[13,15-18,39.48] Drug therapy may also initially be in the best interest of the anxious and panicked pet until it can learn to better cope with owner departures, and may improve the pet's ability to learn. In one 6-week study, the use of a drug alone (fluoxetine) led to improvement in overall severity in comparison to placebo at all time points; however, statistical improvement was not achieved in as many parameters nor at as many time points as in other studies where behavior modification and drug were combined.[19] In addition, it should be noted that fluoxetine is licensed only for use with concurrent behavior therapy. On the other hand, in another study behavior modification alone appeared to be no less effective than the combination of clomipramine and behavior modification.[20] In this study, clomipramine appeared to have a sustained effect at reducing general activity as well as a modest suppression of attachment-related tendency to seek physical contact. However, the groups in this study were small; there were differences at baseline, and an extensive behavior modification program was utilized which included denying access to the bedroom, stopping all interaction one hour prior to departure, and physically separating the dog from the owners with a dividing door or gate when the owner was at home. However, at least from an American perspective, the prognosis appears to be poorest when more instructions were given (>5) and owners are less willing to comply with tasks they find more difficult.[39]

EVIDENCE-BASED MEDICINE

Evidence-based decision making is a means of providing the best information and treatment options that evidence has to offer. The validity of the information, the fundamentals of all clinical trials and their trial design, and the application of statistics is necessary to properly appraise the evidence. The final therapeutic approach should then be selected using the evidence combined with the clinician's expertise as to the patient, client, and problem. Assessing outcomes further enhances the process. In veterinary medicine; however, there is limited availability to the process.[49] Many sources of veterinary information fall in the poorest (D) level including personal experience, colleague opinion, non-veterinary expertise, continuing education notes, textbooks, internet, or inconclusive studies of any kind. Studies based on in vitro research or from another species also likely fall into this category. At the other extreme, the most desirable level (A) are systematic reviews with homogeneity or randomized controlled clinical trials (RT). Where the assessment of multiple randomized controlled clinical trials is not possible, then a single randomized control trial with high confidence would be the next best option. At the next level (B) are systematic reviews of cohort studies with homogeneity (comparing groups that received the treatment to those that did not), an individual cohort study or lower quality RTs, or outcomes research and population studies. Case series or poor quality cohort or case control studies would get a C rating.

DRUG THERAPY FOR SEPARATION ANXIETY – SHOW ME THE EVIDENCE

As mentioned, drugs can be used in conjunction with behavior modification to reduce the pet's anxiety, improve learning, and help it to better cope with owner departures especially during the first few months of training. In placebo-controlled studies using fluoxetine plus behavior modification, a significant improvement was achieved over behavior modification plus placebo.[13,15,17,18,48] While these antidepressants may achieve peak plasma levels within hours, this does not reflect their therapeutic effect since reuptake inhibition may induce downregulation of post-synaptic receptors that are responsible for the clinical effects. Therefore, while improvement may be seen within the first week or two of the program, treatment should be maintained for at least 2 months to determine the full effect of the drug plus behavior program.

Fluoxetine

Fluoxetine is a selective serotonin reuptake inhibitor (SSRI) that has recently been licensed in the United States for the treatment of separation anxiety in dogs at a dose of 1 to 2 mg/kg per day in conjunction with a program of behavior modification. Prior to the North American trial, pharmacokinetic studies were performed indicating a T_{max} of 1.8 hours for fluoxetine and 12 hours for its active intermediate metabolite norfluoxetine, and a clearance half life of 6.2 hours for fluoxetine and 49 hours for norluoxetine. A multi-site placebo-controlled dose determination study of 394 dogs at 47 veterinary practices in Europe (which is as yet unpublished) comparing various doses of fluoxetine plus behavior modification to placebo plus behavior modification, determined that the optimum dose that achieved significant improvement over the placebo group without any significant side effects was 1 to 2 mg/kg per day.

In a multi-center 9-week North American trial of 197 dogs using a dose of 1 to 2 mg/kg (0.45 to 0.91 mg/lb/day), after 8 weeks of treatment with fluoxetine chewable tablets (FCT) plus a behavior modification plan (BMP), there was a significant improvement in overall severity scores over the placebo plus BMP group: 73% of FCT plus BMP dogs were improved compared with 51% in the placebo plus BMP group. In fact, after the first week of treatment 42% of dogs treated with FCT plus BMP had improvement in overall severity scores compared with 18% of the placebo plus BMP group. Destructiveness, vocalization and restlessness were all significantly improved at each week of the trial except for week 3 for destructiveness and weeks 1, 3, and 4 for vocalization. In the safety evaluable group there were 229 dogs. Calmness, lethargy, and anorexia were the most commonly reported side effects. No significant changes in any of the blood parameters were seen through the course of the study. The beef-flavored chewable tablets were also determined to be palatable to treated dogs and easy to administer.[15]

In a second multi-center 6-week trial of 208 dogs in the US and Canada, the efficacy of fluoxetine chewable tablets (FCT) was compared with placebo in the treatment of separation anxiety. Overall severity scores were improved over the placebo group at all weeks with significant improvement at weeks 1 and 4. Destructiveness was also improved at each week with significant improvement at weeks 4 to 6, while urination and salivation were also improved at each time point but statistical significance was not achieved. This trial therefore indicated that there was a measurable drug effect but that greater and more significant improvement could be achieved using a combination of behavior modification and fluoxetine. In fact, the drug is recommended and licensed for use only in combination with a behavior modification program. [19]

Although there are no other licensed uses for fluoxetine in dogs, there is also evidence that fluoxetine may be useful in the treatment of generalized anxiety disorders.[50] Fluoxetine has also been demonstrated to be effective in the treatment of compulsive disorders in dogs.[51-54]

If anorexia or weight loss is significant, the dose may need to be reduced. SSRIs should not be used concurrently with other antidepressants or monoamine oxidase (MAO) inhibitors (eg, selegiline and amitraz). Since SSRIs inhibit cytochrome P-450 enzymes, they can lead to increased toxicity when combined with drugs that are metabolized by these enzymes.

Clomipramine

Clomipramine is a tricyclic antidepressant (TCA) that inhibits serotonin reuptake and, to a lesser extent, noradrenaline reuptake. It also has anticholinergic and antihistaminic effects, which might account for some its side effects, such as lethargy, dry mouth or gastrointestinal upset which are generally mild and transient.[13,17] Tricyclic antidepressants are contraindicated with cardiac disease, glaucoma, where urine retention is a concern. However, clomipramine appears to be associated with less urinary stasis, cardiac disease, and anticholinergic effects in dogs in comparison to its use in humans because of its shorter half-life and its rapid elimination. In addition the ratio of clomipramine to desmethylclomipramine is higher in dogs (3:1) than humans (1:2.5) and desmethylclomipramine is likely responsible for most of the noradrenergic and anticholinergic side effects.[54] Clomipramine has a time to peak concentration of about 1.6 hours for clomipramine and 1.2 hours for its active intermediate metabolite desmethylclompramine, and has a half life of about 4 hours and reaches a steady state in about 4 days.[55] As with other drugs in this class, 4 to 8 weeks of therapy is generally recommended to fully assess therapeutic effects.

Clomipramine is licensed for treatment of separation anxiety in dogs in a number of countries in conjunction with a program of behavior modification at a dose of 1 to 2 mg/kg twice daily. However, in the US the label claim recommends a dose of 2 to 4 mg/kg either as a single daily dose or divided twice daily, although most published studies have utilized twice daily dosing.[13,14,16-18,48] Studies have demonstrated that clomipramine in conjunction with behavior modification provides significant improvement over placebo plus behavior modification. In one study after the first week, 47% of dogs receiving clomipamine plus behavior modification showed improvement compared with 29% of the dogs receiving behavior modification alone.[13] After 4 weeks the improvement with clomipramine plus behavior modification had reached 63% compared with placebo alone and this trend continued through 8 weeks of treatment although significance was not achieved.[13] More dogs were improved in the clomipramine group for destructiveness, urination and defecation but statistical significance was not always achieved.

In a follow-up study of 76 cases, 12 dogs had been on ongoing treatment for over 13 months with no adverse effects or relapse, and 10 of the dogs showed further improvement. Of 22 dogs with complete resolution when the drug was ceased, 13.6% relapsed. Therefore, it is likely that some dogs will require or benefit from a much longer course of drug therapy.[14]

In some countries clomipramine is also licensed for the treatment of other anxiety disorders and compulsive disorders. Clomipramine, in combination with BMP, has also been used for the treatment of storm phobias in combination with benzodiazepines on the day of storms.[56] Clomipramine is also effective in the treatment of compulsive disorders in dogs.[53,57-59]

Tricyclic antidepressants should not be used concurrently with MAO inhibitors such as selegiline or amitraz and should be used cautiously in pets with seizures.

SSRI or TCA

When comparing a TCA such as clomipramine to an SSRI such as fluoxetine, the potential for side effects is theoretically greater with the TCA since there is the potential for anticholinergic, antihistaminic, and alpha-adrenergic blockade as well as both serotonin and noradrenaline reuptake blockade, compared with the serotonin selective reuptake inhibition of fluoxetine. In one study amitriptyline led to tachycardia and hypotension compared to fluoxetine.[60] However, in several trials, clomipramine has been shown to have no cardiac effects on healthy dogs and no significant effects on intraocular pressure.[61,62]

DAP

DAP is a synthetic version of the intermammary appeasing pheromone that has been identified in the lactating bitch. A diffuser formula of DAP was compared to clomipramine in 67 dogs showing signs pf separation anxiety. All dogs received behavior modification and the owners were given either clomipramine and placebo DAP or DAP and placebo clomipramine. Behaviors improved in both groups over a 28-day trial with no significant difference in overall improvement between the two groups.[0]

Other Therapeutic Options

Where a more immediate response is required SSRIs might be combined with benzodiazpines or used concurrently with aromatherapy or other natural products such as l-theanine or melatonin that might help to reduce anxiety.[63-66] However, no controlled trials have been done to assess the efficacy of benzodiazepines or other therapeutic agents in the treatment of separation anxiety. Fluoxetine and clomipramine might also be used concurrently with DAP.

Selegiline might be indicated in the older dog with signs of separation anxiety that might also be associated with cognitive dysfunction. However, selegiline cannot be used concurrently with SSRIs and TCAs. Recent European studies have also shown that selegiline might be useful in dogs with chronic states of stress and high anxiety states, especially those associated with autonomic arousal and stereotypic behavior. In these dogs, prolactin levels were found to be elevated.[22] Selegiline was also effective in four dogs with social and sound phobias at a dose of .5 mg/kg per day along with a combination of propranolol and alprazolam for days with thunderstorms or fireworks.[67] In a preliminary study, selegiline and alpha-casozepine both led to significant improvement in anxiety disorders of dogs.[66]

Reference are available from the author upon request (numbering continues from Part 1 of this two-part article).

BEHAVIOR MODIFICATION CASE MANAGEMENT IN GENERAL PRACTICE

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Most of companion animal veterinary medicine exists to provide services to owners who largely enjoy their pet's behaviors. It is important for us to help clients that are having problems with their pets' desired behaviors. When that bond gets strained or broken, the pet is at risk of losing its home or life and the veterinary profession is at risk of losing a patient. Depending on the level of commitment and knowledge of the individual general veterinary practice, every office can provide some level of veterinary behavior services.

BEHAVIOR SERVICES FOR ANY PRACTICE

Any practice can provide owners with general advice on selecting and raising physically **and behaviorally** healthy pets, which also make better patients and clients for the practice.

First Vet Visit

- Sets tone for relationships with pet and owner
- Have enough time: book two time slots
- Use checklist to systematically cover items
- Decide what each team member will cover
- Assure good/great experience for puppy/kitten
    - Use highest value goodies and fun toys
- Send home puppy/kitten kit & include:
    - Behavior educational material
    - Appropriate toys, socialization treats, etc.

The 8- to 14-Week-Old Puppy Must Learn:

- Bite inhibition
- Housetraining
- Appropriate chew items
- Listen to owners
- Be left all alone
- Tolerate veterinary handling
- What/who will be part of its life (other dogs, cats, kids, different people, etc.)

New Kitten Must Learn:

- Not to bite or claw people
- Appropriate litter box use
- Appropriate places to scratch
- Tolerate veterinary handling
- What/who will be part of its life (other dogs, cats, kids, different people, etc.)

Provide or send clients to programs to teach owners how to properly **socialize** and raise new kitten or puppy. Puppy socialization classes (start at 10 to 12 weeks of age and avoid unwarranted fear of canine sensitive period overlapping with primary veterinary vaccination period as this is not realistically a significant problem with good infectious disease protocols in place) or at least "puppy parties." Do your "due diligence" and if your practice provides it be sure the instructors are well trained; if you send clients to an outside provider, be sure that provider is well educated, experienced and humane (they will reflect on your practice).

- Once adopted, puppy kindergarten/socialization classes can help start puppies and owner off "on the right paw."
- Start at at 10 to 12 weeks of age to take advantage of socialization period in puppies that ends at 16 weeks (4 months).
- Routine handling and mock "exams" along with treats and praise
- Helps to make a more tractable future patient and owner more bonded to their pet
- Basic lure/praise based obedience training can be of great help for dogs
- Start early before too many problems develop
- Appropriate collars, halters, and harnesses such as Gentle Leader® or Easy Walk® can be important training aids.
- Training should be humane, effective and fun.
- Progressive techniques should not rely primarily on the strength of the trainer or methods that cause pain and undue distress.
- Practice must inquire about and "triage" behavior presentations from pets of all ages to appropriate provider (unruly/disobedient vs. behavior problem).
- Identify medical presentations with untreated **underlying behavior causes** for example:
    - Traumatic wounds inflicted by another animal (eg, inter-dog/inter-cat social aggression, aggression to unfamiliar dogs)
    - Self-trauma (eg, panic attacks, compulsive disorders)
    - Foreign body ingestion/enterotomy (compulsive behavior, pica, inappropriate chewing, etc.)
    - "Backyard" dog or "outside" cat (increased risk) (unmanaged indoor behaviors such as chewing, house-soiling, destructive behavior, unruly, etc.)
- Work up potential behavior problems to rule out physiological ("organic") disease and/or get baseline lab database.

MAKING A GOOD REFERRAL

When should you refer your client to a Veterinary Behaviorist rather than a trainer? A progressive skilled trainer may be fine for:

- Untrained dog:
    - Needs "well care" such as COME, SIT, DOWN, DROP-IT, basic initial housetraining (not resistant adult IE problem) etc.
- Dog is mostly just unruly for example:
    - Jumping up on people
    - Runs away when called & does not listen to owners
    - Mouthing owners in play/excitement (barking at owner for attention, not only when alone),

analogous to child just needing to go to a decent credentialed teacher at good public school.

If a behavior problem presents, a professional trained for problem animal behavior will likely be needed, preferably a boarded veterinary behavior specialist (Diplomate ACVB).

- Trained and credentialed to work up and assess any kind of animal behavior problem (not just dogs) and have **all treatment modalities** available to use as most appropriate.
- Analogous to a child having been in good public school (or missed out) BUT now needs an Individual Education Program (**IEP**) developed (= treatment plan) incorporating appropriate components.

Know Your Behavior Professionals
Credentials/representations:

- **Meaningful** (Academic training and experience required, certification process)
  - Diplomate ACVB (Veterinary Behaviorist)
  - Certified Applied Animal Behaviorist (CAAB)
- Generally **not meaningful** (self promotion with no universally accepted criteria)
  - Behaviorist, dog psychologist, animal behavior specialist, "dog whisperer," offers: "behavior modification," "private" certification
- Generally legal to make these claims as long as not a veterinarian

Best referrals to a board-certified Veterinary Behaviorist have:

- Motivated owners with appropriate expectations and understand the need to commit some time & financial investment in their pet to solve behavior problems (most are chronic conditions and unlikely to be an "easy fix").
- "Organic" problems have been ruled out (though, again, not typically required if problem appropriate).

Finding a Behaviorist in your area:

- American College of Veterinary Behaviorists (ACVB) www.dacvb.org
- Animal Behavior Society Certified Applied Animal Behaviorist (most NOT veterinarians but do have credentialing program) www.animalbehavior.org
- Call nearest VMA or Vet School for specialist in your area.
- If no boarded specialist around, you may find a veterinarian with a special interest in behavior problems (eg, AVSAB dues paying member but **no** credentialing program www.avsabonline.org)

Logistics:

- Client will typically call the specialist's office and make an appointment. Like other specialists, Veterinary Behaviorists usually cannot drop their case load and speak with potential owners before appointment.
- History, behavior exam, diagnosis, treatment and prognosis are all part of the behavior appointment.
- Initial appointments are typically 1.5 to 3.5 hours long depending on problem, history and provider.

WHAT HAPPENS DURING A TYPICAL BEHAVIOR APPOINTMENT?

- Detailed History and exam/evaluation
- Diagnosis and discussion with client
- Treatment Plan developed and explained/ demonstrated to owner
- Prognosis at initial visit
- Referral/case summary letter sent to referring practitioner.
- Rechecks and phone follow-up by owner as appropriate.
- If possible fill out specialist's **referral form** to facilitate the referral and summarize your medical & other knowledge of pet's relevant history.
- Give client practice **telephone number** and website (if appropriate) to call specialty practice for an appointment.
- Avoid discussing specific fee amounts ("***appropriate professional fees*** for doctor's time charged in line with other veterinary specialties"). Leave **details to specialty practice** since some clients will only hear the $$ figure without any context of what the value is and what they will get for their money. With the extensive time the specialist spends with your client and their case write-up and management, veterinary behavioral medicine is one of the best values for the money in the profession.
- Send appropriate medical records and lab data **after the appointment** has been made (FAX, mail or via client).
- Call if you feel that briefing specialist would be of extra value or just if you prefer to discuss the case before referring.

PRACTICES WITH MORE RIGOROUS COMMITMENT TO BEHAVIOR SERVICES

- Diagnose and suggest straight forward treatment plans for selected behavior problems-
  - Requires a general practitioner with an interest and **fundamental training in behavioral disorders**.
  - Appropriately trained staff can help teach clients with problems where medication is not used.

- Veterinarian with interest in behavior can diagnose and suggest simple treatments for selected behavior problems, especially when FDA approved medications are available or, at least, well established treatment protocols are published.
  - Uncomplicated dog separation anxiety case (Reconcile® and Clomicalm®).
  - Uncomplicated canine cognitive dysfunction in older dog (Anipryl®).
  - Uncomplicated inappropriate elimination cases in cats and dogs (no FDA approved treatments).

  - Other straightforward anxiety-related, excitable, and destructive behaviors in dogs and cats (no FDA-approved treatments)

RESOURCES

Practitioners and staff who wish to learn more about veterinary behavioral medicine can access various easily available sources including:

Web sites:

- American College of Veterinary Behaviorists: www.dacvb.org
- Dr. RK Anderson's (DACVB and co-inventor of Gentle Leader®) New Animal Behavior Resources Institute www.ABRIonline.org
- Animal Behavior Society's web site with section on Applied Animal Behavior credentialing (primarily if not already a veterinarian): www.animalbehavior.org
- Many others on web but always check sources.

Publications:

- "Starting a Behavior Program": a collection of articles from Veterinary Economics and Veterinary Medicine (800-255-6864)
- *Handbook of Behavior Problems of the Dog and Cat* (Landsberg DACVB, Hunthausen DVM and Ackerman DACVD) 2003 published by Saunders.
- *Puppy Class manual* from Premier Pet Products
- Lifelearn C/D (2002) containing 62 behavior handouts (Landsberg and Horwitz both DACVB) (800-375-7994).
- Pet Behavior Pamphlets by AAHA (800-883-6301).

Join Veterinary Behavior Interest Group:

- American Veterinary Society of Animal Behavior (AVSAB at www.avsabonline.org)
- Go to CE- Many national and regional conferences have behavior available including:
  - AVMA annual meetings (associated ACVB/AVSAB meetings)
  - Western Veterinary Conference (WVC)
  - The North American Veterinary Conference (NAVC)
  - The Central Veterinary Conference (CVC).
  - Local & regional Presentations by Veterinary Behaviorists
  - Annual "Association of Pet Dog Trainers" (APDT) meetings (www.apdt.com)

CHARGE FOR YOUR BEHAVIOR SERVICES

- Some of general behavioral advice noted above (eg, for all practices) may be included as part of your regular client services and not charged for additionally, but help you stand out from other practices and generate revenue from products and classes.
- More involved behavior workups, diagnosis, and treatment plans cannot be done during a routine medical exam (just like human patient with psychological problems can not be treated properly as part of routine yearly exam) and a distinct, longer behavioral appointment must be made. Charge will depend on doctor time and can be increments of routine appointment fee. It is often best to schedule these appointments just before lunch or at the end of day (schedule like euthanasia time slot) in case it runs over a bit from the anticipated time slot. Use an interested technician (send to CE, assign reading, join Veterinary Behavior Technicians Association, etc.) to help with client education/explain treatment plan just as we do with post op physical therapy, home dental care education, etc. The perceived value and compliance increases as you charge for your expertise and time. Use handouts (see above) along with well documented products (eg, Gentle Leader "system" packaging) to leverage your appointment time.

PROVIDING VETERINARY BEHAVIOR SERVICES

- Positive:
  - Additional **profit** center with some **profitable products**.
  - Helps further bond your clients to your practice.
  - Helps make for patients that are easier to handle.
- Negative:
  - Time consuming and hard to charge for that time.
- Even if you have a special interest in behavior, consider referring certain problems that are resistant to therapy; complex presentations/history; **aggression**, especially towards people
  - Caution with aggression between resident dogs-human at great risk when breaking up fights!
  - Use a Veterinary Behavior **Specialist** if possible.
  - Possible liability issue if you refer to lay person (always best to refer "up" in the profession).

SUMMARY

- **Any practice** can benefit and NEEDS to participate
- The level of integrating behavioral services only limited by **interest and training** of doctors and staff in the practice.
- Like with other veterinary specialties, **refer cases** that your practice is not trained to diagnose and treat; develop a good **referral system** to the nearest well-trained and effective behavior specialist.
- Help preserve and foster the human–animal bond that feeds the rest of your practice. Your clients will love it!

SPEAKING DOG – UNDERSTANDING HOW DOGS SIGNAL

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The uniting feature that connects all social vertebrates is the extent to which they signal non-verbally. Communication involving ritualized displays or graded signals is used to confirm or reject information received from others in social interactions, to indicate species, sex, and sexual receptivity, to signal about issues pertaining to status, and to otherwise negotiate all social interactions. As such, communication can involve such instantaneous behaviors as tactile and visual displays. These are relatively "short-distance" signals. Vocal communication is also instantaneous, but may reach over longer distances. Verbal communication is only one variety of vocal communication, and both of these may pale when the full story of olfactory communication is written. Certainly, olfactory and pheromonal signals provide information that can be assessed over distances and across time.

When assessing any communicatory structure it is important to realize that signaling involves a set of rules that will be shaped by the evolutionary history of the species. The story of canine domestication is the story of work and work-related tasks. The story of feline domestication is the story of rodent and vector borne diseases and their prevention. These two divergent paths to domestic lifestyles have been shaped by, and in turn have continued to shape factors like reproductive schedules, fecundity, age at first reproduction, age at sexual and social maturity, composition of family or group units, and social interactions within these units. To understand such behaviors it is critical to understand the component signals as they are used to communicate with conspecifics. Table 1 provides an introduction to canine signaling.

WHY UNDERSTAND SIGNALING?

Understanding signaling is essential to taking a good history in behavioral medicine. The client tells you that "Fluffy is aggressive." This is a simple declarative statement, except we have no idea what it means. For one client, it can mean that the year-old dog was—and had been since puppyhood—tethered to a tie-down 23 out of 24 hours and tried everything, including grabbing the owner and leading her to the ball, to solicit play during her one hour of freedom. The action with the teeth seemed "aggressive" to the client and her desire to play with the dog decreased as the size of the dog and the desperation with which the dog sought play grew.

There is only one way out of this problem: collect data on the actual behaviors. Watch the dog when you are talking to the client, ask the client to interact with the dog the way they normally do, videotape the dog while you are doing this so that you can review the tape leisurely and learn something, ask the client to videotape the dog at home doing its normal routine, ask about specific behaviors. If you are unsure of something, put the dog in a different situation. If the client tells you that the dog barks when he sees other dogs on the street, ask if it's a "happy," multi-toned, high-pitched, greeting bark, or a sharp, repetitive bark often associated with distress, or a low, decrescendo, menacing bark. If the client says, "I don't know," thank them for their honesty and take the dog for a walk. Don't make it the client's responsibility to be omniscient. Let them know early on that not only is it okay to not know something, but that it's important for you to know when they are unsure so that you can collect the data. You don't have to go to the client's house to do this, and given that you automatically change the social environment when you do so, you might want to save home visits for situations needing further clarification. You can often do just as well and sometimes better with videotape of ordinary activities.

It's the difference between a judgment or interpretation and an **event** that is so critical in behavior and behavioral medicine. This means that you must see the dog and his or her behaviors. It's good science to do so since in behavior and behavioral medicine the data are the behaviors, and there is no excuse for not collecting the data to the extent possible. Part of doing science is to evaluate the quality of your data and ask if they are suitable for answering the question you asked. So when someone tells you that the dog is "shy," "fearful," "aggressive," "confident," "dominant," "submissive," "bored," "angry," et cetera, you should always, always ask yourself if what you were told contained information worth having. You should always confirm your assessment by asking: "Exactly what did he do? Was his tail up or down? Where were his ears? Was he making any sounds? What behaviors does he exhibit that makes you think he is "bored" (or "angry" or "shy"...)? If he is in XYZ circumstance, what exactly does he do and how often does he do it?" If the dog's person cannot answer these questions, well, you're at an excellent place to start: you know exactly which data they need to go home and collect.

EARLY INTERVENTION: ROUTINE SCREEN FOR BEHAVIORAL PROBLEMS

Most veterinarians obtain a routine history about physical complaints and concerns when they examine any dog or cat regardless of whether that pet is newly adopted or has been a beloved family member for a decade. We are all getting better about screening for geriatric health problems as we learn more about keeping pets happy and healthy for longer times. But the single biggest "health" problem faced by pet dogs and cats is still associated with behavioral pathologies or unmet behavioral expectations. Modern veterinary care should include routine screening about specific behavioral complaints in addition to routine questions that alert veterinarians to potential somatic medical problems. If we can ask "Any vomiting, diarrhea, changes in appetite?" we can also ask "Any inappropriate or undesirable chewing, any growling, any odd behaviors?" If we do this, we accomplish the following goals:

1. We initiate a dialog with the clients about behavior. This lets them know that not only is behavior important, but it is central to good veterinary care. Clients will then feel comfortable asking their veterinarian about behavioral issues. Such dialog represents our best chance for learning of a client's behavioral concerns before these concerns threaten the pet's life.
2. We establish a baseline of the particular pet's behaviors. Such a behavioral profile will allow us learn "normal" for that pet so that we have a context in which to evaluate behavioral change or client complaints about behavior. This is exactly what we are doing when we recommend routine laboratory evaluation for healthy pets...if we never knew when the pet last had a creatinine within the reference range it is difficult to know how long the creatinine has been elevated. Length of dysfunction—whether the dysfunction involves a "medical" or a "behavioral" complaint—can affect prognosis, and the extent to which this is true in behavioral medicine is profound.

A basic questionnaire for dogs that can be completed at each visit should be used (See: Overall, K.L. Manual of Clinical Behavioral Medicine for Small Animals, Elsevier, St. Louis, 2008, for one example). This questionnaire should be used at any and all visits to check if the clients have any questions or complaints. You have to remember that the clients might not even know that they have questions or complaints because they do not know what "normal" is. Also, if anything, myths about breeds, behavior, nature, and nurture are far more insidious in the client community than in the veterinary community. Finally, it's important to remember that the clients may not know what normal behavior is, or that they may be uncomfortable with a behavior, but not know how to ask if it is abnormal. This and more detailed questionnaires will give clients the vocabulary and opportunity to discuss their pet's behaviors with their veterinarian in an efficient and progressive manner.

References are available from the author upon request.

Table 1. Canine Signals

Signal	Circumstance Information
Barking	Alerting/warning Attention-seeking
Growling	Warning Distance-increasing
Crying, whimpering, whining	Et-epimeletic
Howling	Elicit social contact Anxiety situations (social contact = reassure)
Moans	Pleasure, contentment
Tail and ears up; forefoot in front of other	Alert, ready to participate
Direct gaze	Challenge Confidence Absence of threat Distance-increasing
Averted gaze	Fear 'Cowardice' (caution) Deference Absence of challenge (not the same as deference for confident, high-ranking dogs) Distance-decreasing signal
Belly presented	Deference - if neck back and other solicitation cues given Disengagement - if inguinal area and, or chest covered may become aggressive if pursued Relaxation - if flaccid
Tail tucked when belly presented	Fear/submission
Tail tucked when belly presented with urination	Profound fear/'submission'
Grin	Deference Distance-decreasing signal

Signal	Circumstance Information
Piloerection	Arousal associated with anxiety, fear, aggression Distance-increasing
Piloerection restricted to neck or tail region	Confident dog
Rigid stance, stiff torso musculature	Confidence and intent to interact (may not be aggressive) Distance-increasing
Tail above horizon	Confident High 'status'
Tail below horizon	Less confident Lower 'status' Deference Fear
Tail wag	Willingness to interact
Tail tip wag; stiff	Confident Assertive Offensively interactive
Neck erect or arched	Confident Challenging
Ears erect	Alert Confident
Ears back	Fear
Ears vertically dropped	Deference 'Submission' Low 'rank' Anxiety
Snarl/growl with only incisors and canines apparent	Confident Offensively aggressive Distance-increasing
Snarl/growl with all teeth and back of throat apparent	Defensively aggressive Fearful Distance-increasing
Body lowered	Defensive Distance-decreasing Fearful Deferential Relaxed
Licking lips, flicking tongue	Appeasement Et-epimeletic Distance-decreasing Anxious (and solicitation of reassurance; derived from et-epimeletic)
Raising forepaw	Distance-decreasing Solicitation of attention Deference (off balance)
Paws out, front end down, rump up, tail wagging	Body bow, invitation to play
Perpendicular posture	Challenge Confidence
Mounting or pressing on back or shoulders of another dog	Challenge Marking, claiming Asking a question about interaction; information seeking
Licking at corner of another dog's (or person's) mouth	Et-epimeletic Deference Solicitation
Blowing out lips/cheeks	Anticipation (positive or negative) Anxiety (if very fast)
Popping or snapping of upper and lower jaws (bill pops)	Capitulation, intention to comply as a last resort

UNDERSTANDING CATS WHO FIGHT AND WHY THIS AFFECTS LITTERBOX USE

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FELINE AGGRESSION AND ASSOCIATIONS WITH ELIMINATION DISORDERS

Feline social systems differ from those of dogs in many ways, and their history with humans is worth discussing. Cats were likely never truly “domesticated.” Ancestral cats are not very different from modern cats in either size or habit. Cats have historically been found near and around human settlements, because where there are people there is stored food, and where there is stored food there are rodents. A mouse or a rat makes a single meal for the cat on the go. Accordingly, modern cats are solitary hunters who live in matrilineal (mother focused) social groups. Unlike the situation with dogs, we have not substantially altered anything about their social behavior until fairly recently. Again, unlike dogs, when we started to purpose-breed cats to develop cat breeds/breed fancy, we focused on changes in color, coat texture, coat length, tail or ear shape, an so on, not on enhancing specific jobs that different breeds do, as is the case with dogs. It is not surprising that the types of inappropriate aggression witnessed by clients differ from those seen in dogs and that they are understandable given the evolutionary context of feline social systems and the developmental context of sensitive periods. This is one of the reasons that it is often difficult for clients to understand—or even to recognize—intercat aggression. When complaints about feline elimination do not resolve with routine care and intervention there is a high probability that the elimination issues are interwoven with those involving intercat aggression. A complete history, including a viewing of family photographs and a video-tour of the cats’ ‘normal’ interactions will allow the clinician to understand these co-morbid interactions.

INTERCAT AGGRESSION

Normal aggression between cats is common only if the cats are toms. In most wild, feline social systems, few males mate with most of the females. The skewed sex ratio in the breeding population is induced and maintained by vigilance and aggression on the part of the males. There is an additional olfactory component of spraying and non-spraying marking that contribute to the aggression and relative “status.” The aggression exhibited by males in these circumstances is classic and involves flattened ears, howling, hissing, piloerection, threats using eyes, teeth, and claws and combat. Early neutering (prior to 12 months of age) decreases or prevents fighting by 90%. It is not clear if very early spaying and neutering programs would further reduce this, but given the hormonal facilitation of the aggression one would hypothesize that this would be the case.

That said, true intercat aggression—which is far more common and more likely than is territorial aggression, with which it is often confused—is pathological and is more commonly based on conflicts within social hierarchies than it is with sex. Cats begin to become socially mature some where between 2 and 4 years of age. At this time, some cats may begin to challenge others. Problems arise when one cat will not accept lack of engagement by another cat. Responses include passive aggression (staring and posturing), active aggression, and marking. Cats that consider themselves as more equal are less likely to participate in overt aggression - expect covert aggression (See Table 1 for a sample format by which to understand the variants of this form of aggression). Intercat aggression is extremely complex, often subtle, and under-appreciated.

Cats that are afraid of other cats can be spontaneously afraid of them or be afraid because they have been attacked, and may develop fearful behavior or fear aggression as sequelae. Co-morbidity of diagnoses should alert the client or clinician to explore which came first.

Table 1. Heuristic Model for Thinking About Phenotypic Patterns of Feline Aggression:

Potential Axes:

- Overt v. covert aggression
- Active v. passive aggression
- Offensive v. defensive aggression

Sample Scenarios:

- Overt, passive, offensive aggression: confident cat staring when another enters room
- Overt, passive, defensive aggression: less confident cat leaving room or backing up and withdrawing into smaller space, tail tucked vocalizing
- Covert, passive, defensive aggression: vanquished or less confident marking with mystacial glands in boundary areas or areas from which cat had been displaced
- Covert, active, offensive aggression: vanquished or less confident marking with urine or feces in boundary areas or areas from which cat had been displaced
- Overt, active, offensive aggression: chase and attack using teeth and accompanied by vocalization by resident cat toward new cat in environment
- Overt, active, defensive aggression: attack or response using hitting and or swatting while leaning back or avoiding further pursuit
- Covert, active, defensive aggression: withdrawal and marking of restricted area by victim cat
- Covert, passive, offensive aggression: displacement or theft of “bully” or higher ranking cat’s toys, bed, food, or hidden copulations (?), accompanied by non-elimination pheromonal marking

Cats that react as if there is a challenge about social status when there is none are reacting inappropriately and out-of-context. If there is a challenge (staring, blocking, hackles up, hissing, swatting, growling, etc.) of any kind, a reaction might be appropriate, but it is important to remember that as for people, many normal social behaviors in cats have rules. If one cat responds to another cat's stare or approach by leaving, tracking that cat down and becoming more overtly aggressive, this would be an inappropriate response. Most aggression in cats is far more subtle than it is in dogs, and because of this, may be more damaging to household situations.

Most intercat aggression about which clients complain occurs between housemates, and it may occur more commonly between different sex housemates, in contrast with dogs. Also, because feline systems are matrilineal, aggression may only become apparent after the loss of a 'matriarch' or cat fulfilling this role. It is not unusual for cats dogs to have lived in relative harmony together for 2 years before there are problems because the development of these problems reflects the intrinsic change that all social animals experience when the become socially mature.

Challenges can involve staring, vocalizing, or outright aggression. They can start with staring and escalate to aggression. Regardless, it is important to treat the problem as soon as it becomes apparent. The longer that the problem is allowed to persist, the worse the cats will get.

In profound cases of intercat aggression, the situation is not simple. This is especially true if multiple cats are in the household because cats form coalitions. This means that a cat who has been neutral to another specific cat may change his or her behavior depending on the addition or loss of new cats and the shifting of coalitions. Also, these relationships are not absolute. They change with age, health, and—most importantly—*behavioral context*. The manifestations of the relationships can be affected by the people who are present and by how those people interact with them. Some relationships apply only to feeding and sleeping orders. A cat who challenges one cat may not care about another cat in the household that, to all outward appearances, seems to act the same and be the same age and sex. Chances are they are not acting identically, and it is in the subtleties that the problems with the relationship occur.

Treatment of intercat aggression focuses keeping everyone safe, and on setting and maintaining a new social order where no individual is forced to sustain constant threats. Generally, reinforcement is given to the cat who is behaving most appropriately. Clients can most easily determine this by videotaping their cats and working with their veterinarian to understand what is ongoing between the cats. Identification of problem cats and those who are really normal is actually pretty easy if you can watch the cats in an unbiased manner. This is the advantage of videotape over real-time. The specifics of treatment follow.

First, please tell your clients to never physically punish these cats. All you will do is to raise their level of distress, and they might feel that they have to fight off the clients. Clients are often injuring when disciplining or separating fighting animals. You could make a bad situation worse by further causing the involved cats to be reactive and to learn that you are a threat.

Second, if at all possible, never reach between two fighting animals. Most people have good intentions and want to separate fighting animals to prevent injury to them, but if clients place their body parts between the animals, they may be accidentally injured. Rather, if the client knows that he or she has a problem with the cats, he or she should watch them like hawks any time they are together and keep cardboard, a broom, a bucket of water, a hose, or a blanket handy. These are all "remote control" items that can be used to separate the cats safely. If no small children, high-strung humans, or nervous animals are in the house, a loud noise, like that generated by a foghorn, can also help to separate animals for whom nothing else works, but this is drastic recourse and should be used cautiously.

Screaming by Humans, Particularly Young Humans, will Worsen the Situation

Generally, once the cats are apart, they start to calm down, and the aggressor can be moved to a location that is safer for everyone. Please remember that because of the unique reactivity of the feline posterolateral hypothalamus (PLH) and ventromedial hypothalamus (VMH), cats can stay reactive for 24 to 48 hours and that the clients may have to banish these cats while still protecting themselves. Most clients would find it easier to remove the victim, but this is not ideal. By removing the victim—instead of the aggressor—you may enhance the 'helplessness' of the victim in the eyes of the aggressor. You don't want to do this, if possible. Still, it is important to remember that any animal that is injured hurts and is frightened. These animals can bite without being malicious. Clients can avoid this by transporting victims and aggressors using blankets and boxes.

Environmental and social manipulation, classic passive and active behavioral modification, and pharmacological intervention (see Table 2) all have roles in treating intercat aggression.

MEDICATIONS

Benzodiazepines, while humanly abusable, can be excellent drugs for some cats who have joint elimination/aggression problems because of underlying nonspecific anxiety that results in a decrease in outgoing behavior in the affected cat. Clients should be advised to watch for any signs associated with hepatopathies, although these are extraordinarily rare. The exact mechanism of action of the benzodiazepines (eg, diazepam, chlordiazepoxide, clorazepate, lorazepam, alprazolam, and clonazepam) is poorly understood. At low dosages, benzodiazepines act as mild sedatives, facilitating daytime activity by tempering excitement. At moderate dosages they act as anti-anxiety agents, facilitating social interaction in a more proactive manner. At high

Table 2. Useful Medications (Brand Names are those in the US)

- Alprazolam (Benzodiazepine; Xanax) – for general calming, a panicolytic effect, and for encouraging affiliation: 0.025–0.050
- Amitriptyline (TCA; Elavil) – for the victim or aggressor with non-specific anxiety: 0.5–1.0 mg/ kg PO q 12–24 h
- Buspirone (NSA; BuSpar)–for the victim, only; may make more outgoing and situation resolves with some overt aggression: 0.5–1.0 mg/kg PO q 12–24 h
- Clomipramine (TCA; Clomicalm) – for the victim or aggressor with more specific anxiety: 0.5 mg/kg PO q 24 h
- Diazepam (Benzodiazepine; Valium) – for the victim, primarily, to make more outgoing and friendlier; for the aggressor if aggression is secondary to anxiety about interaction and increased friendliness will help: 0.2–0.4 mg/kg PO q 12–24 h
- Fluoxetine, paroxetine (SSRI; Prozac, Paxil)–for more specific anxieties involving outburst (fluoxetine) and social (paroxetine) anxieties: 0.5 mg/kg PO q 24 h
- Nortriptyline (TCA; Pamelor) – for the victim or aggressor with non-specific anxiety and sedation with amitriptyline: 0.5–1.0 mg/kg PO q 12–24 h

dosages they act as hypnotics, facilitating sleep. Ataxia and profound sedation usually only occur at dosages beyond those needed for anxiolytic effects. Note that the duration of action of the parent compound, diazepam, and its intermediate metabolite, nordiazepam (N-desmethyl diazepam) in cats is 5.5 h and 21 h, respectively.

Tricyclic antidepressants (TCAs) act to inhibit serotonin and norepinephrine (NE) re-uptake, and can be useful for some cats that spray, some who are averse to or anxious about their litter box, and cats who are experiencing anxiety about heir social situation. Drugs of choice include amitriptyline and its active intermediate metabolite, nortriptyline, and clomipramine. Knowledge of intermediate metabolites can be important: animals experiencing sedation or other side effects with the parent compound may do quite well when treated with the intermediate metabolite alone. For example, cats that become sedated or nauseous when treated with amitriptyline may respond well when treated with nortriptyline at the same dose since the former has two times the NE re-uptake effect of the latter.

Partial 5-HT$_{1A/B}$ agonists (eg, buspirone) have few side effects, do not negatively affect cognition, allow rehabilitation by influencing cognition, attention, arousal, and mood regulation, and may aid in treating aggression associated with impaired social interaction.

The SSRIs (fluoxetine, paroxetine, sertraline, and fluvoxamine) are derivatives of TCAs. These drugs have a long half-life, and after 2 to 3 weeks, plasma levels peak within 4 to 8 hours. Since these drugs act to induce receptor conformation changes—an action that can take 3 to 5 weeks—treatment must continue for a minimum of 6 to 8 weeks before a determination about efficacy can be made. Most of the SSRI effects are due to highly selective blockade of the re-uptake of 5-HT$_{1A}$ into pre-synaptic neurons.

As with all behavioral conditions, the earlier that intercat aggression is diagnosed and treated, the easier it is to treat and the better the outcome (meaning that clients have to live with fewer constraints). The key to treating any behavioral condition well is to communicate as much as we know in a manner that helps the client to participate as effectively as possible in the treatment.

BASIC TREATMENT CHECKLIST FOR CLIENTS TO TAKE HOME

1. **First, keep all cats involved in the intercat aggression separated at all times when not supervised.** If you able to identify the aggressor, the aggressor should be confined to the less desirable room (a spare bedroom, rather than your bedroom; a pen in the heated, well-lit basement; not in the kitchen where the dogs are fed). All other cats should have free-range. Again, in multicat households watch for changes in coalitions of the now re-configured social groups that may not be in the direction that you find helpful!

2. **Bell the cats with different sounding bells.** If the cats are loose you must be willing to supervise them. The bell will tell you when the aggressor is approaching and when the problem animals are close together. They can have a chance to approach each other **if and only if** you are confident that you can control them long-distance, and prevent any injury. Please remember—injury can be physical or behavioral. Of these, the behavioral injury may be worse for many cats who learn to live in constant terror. If you do not feel this way you must separate the cats in a manner that prevents over fighting and covert threats such as stares or urine marks.

3. **Choose an order in which to reinforce the cat based on identifying which cat is behaving the most appropriately. Remember—reinforcement is not about rewarding the pushiest, most 'dominant' cat.** It's about rewarding the cat who is most appropriate so that all the cats get the message that obnoxious behaviors are not rewarded, but calm, non-threatening ones are. When you reinforce the most appropriate cat you feed that cat first, give him or her attention first, give them access to the yard first, etc.

Reinforcing the chosen cat has active and passive components. First, separate the cats as discussed above. Second, enforce the concept that the cat being threatened has the right to exist by feeding him first, letting him out before the others (if they go out), giving him a treat or toy first, playing with first, grooming first, and so on.

You are not imposing a 'rank' order on these cats: instead, you are encouraging the normal types of social deference that would be exhibited by cats under normal conditions. By reinforcing an appropriately behaved cat you encourage the normal fluidity of the social system.

You can also more passively encourage the aggressor to understand that the victim has some status by allowing the victim sleep in a crate in your room, on a bed there, or on your bed, while the other cat is banished to a room or crate outside your room. This has nothing to do with beds and 'spoiling' and everything to do with the fact that access to preferred spots or to attention is a currency.

Regardless of how you decide to work with the cats, each cat needs daily individual attention. The cat that is being reinforced should always get the attention first, in the presence of the other cat if this can be done quietly and without threats or overt aggression. If necessary, restrain the inappropriate cat using a harness.

In this world view, treatment is about both understanding the neurochemical changes that occur with learning and repeated exposure, and about becoming humane. To do this, we must begin to see the world from the cat's point of view, which minimally requires that we let go of labels which may say more about us and our need, than they do about the behavior. The situation with intercat aggression demonstrates why we need to be more mindful of terminology, issues, and approaches which can inadvertently do more harm than good.

4. **Use harnesses with cats, if they are going to be together.** This gives you a quick way to intervene if you need it while gradually reintroducing them to each other when there is no attention being given. For example, watch TV while they both sit quietly, secured at a distance where they can see each other, but not lunge, and connect. If the cat that has been problematic stares at the cat you are trying to reinforce, gently turn his head away from the other cat and towards you so that he can take his cues from you. If the cat that you are trying to reinforce stares at the other, ignore him or her if the other cat doesn't react. If the other cat does react, interrupt them by asking them to look at you. If this does not work or if the aggression intensifies remove the most aggressive cat and banish him or her. If the cat that you are trying to reinforce stares at the other cat and the other cat looks away, reward them both with food treats—that is exactly the type of fluid and flexible behavioral relationship you are trying to reinforce.

5. **Anti-anxiety medications may help some cats that otherwise are not able to succeed in this program.** Please remember, if it's decided that medication could benefit your cat, you need to use it **in addition** to the behavior modification, not instead of it. Newer treatments involving a synthetic analogue of feline cheek gland secretions (eg, pheromones like Feliway™) show some promise for spraying that either has recently started and is related to the introduction of a new individual (human or animal), or to disruptions in the colony scent. Few excellent studies have been conducted, and the need for such studies is more critical in this situation than in those involving some oral medications because the mechanism of action is unknown, but appears to be relatively general. One peer-reviewed study that has examined the use of Feliway for the treatment of spraying, found that in many cases there was a statistically significant reduction in spraying, but few to no cats stopped spraying all together without the additional of behavioral modification. In some cases the concomitant use of pheromonal agents and anti-anxiety medications may produce a quicker resolution than would be produced by either alone.

References available upon request. These notes were adapted from: K.L. Overall. Manual of Small Animal Behavioral Medicine, Elsevier, St. Louis, 2008.

COMBINING MEDICATIONS FOR MAXIMAL EFFECTS

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RATIONALE

The addition of psychotherapeutic agents to routine behavioral treatments, such as behavioral and environmental modification, has lead to better and faster treatment outcomes. In addition to facilitating better treatment of domestic animals and humans, psychopharmacological developments have permitted hypotheses about underlying mechanistic pathology to be tested. Mere treatment of non-specific behavioral complaints and signs is outdated (eg., treat barking by cutting the vocal cords) and has been replaced with an approach that includes ensuring that you meet the criteria for diagnosis, prior to treatment, followed by treatment that addresses the specific mechanism underlying the neurochemical contribution to the pathology.[1]

The use of medication should occur and is most effective as part of an integrated treatment program. There is no substitute for the hard work involved in behavior modification; however, some medications may be able to make it easier to implement the modification.[2,3,4] Those seeking 'quick fix' solutions will doubtless be disappointed: inappropriate drug use will not alter the processes or environments that produced the behavior. While medication, alone, may render an animal globally less anxious, if the animal is still being provoked by social or physical environmental stimuli the benefit of treatment with medication will be minimized. It is partly this facile and inappropriate use of medication that has led many practitioners to falsely believe that medication does not work. Nothing could be further from the truth: the newer serotonin-affecting medications, protective nutraceuticals, and enhanced dietary regimes have a huge potential improve life for troubled pets and their distressed people. In fact, rational drug use should now minimally be considered part of basic humane treatment of our patients.

ADVERSE EFFECTS

The neurotransmitters affected by behavioral medications are acetylcholine, serotonin, norepinephrine (noradrenaline), dopamine, gamma amino butyric acid (GABA), and excitatory amino acids. Common adverse effects of psychotherapeutic drugs are usually caused by a blockage of the muscarinic acetylcholine receptors, which have diffuse connections throughout the brain. These 'common' side effects are actually quite rare and generally manifest themselves as transient changes in GI function or heart rate. If these side effect ARE NOT transient, clients need to understand that their pet may be experiencing a serious problem. For this reason, it is important to encourage clients to help monitor both their animal's response to the medication and any side effects that they may have. Clients can easily learn to take pulse rates. Slight increases in pulse rate when treated with any medications affecting norepinephrine—as most the anti-anxiety agents do—are not worrisome. Huge, sustained increases are problematic. If clients know that their dog's resting heart rate is 65 bpm and with medication this changes to 150 bpm, they can immediately bring this change to their vet's attention. Likewise, if the increase is minor (65 to 75 bpm) they can relax and not worry. Educated clients will monitor their pets better, will be more willing to use medications and behavior modification appropriately, and will also be less likely to take the veterinarian's time needlessly. While many benzodiazepines (BZ) can be sedative, newer BZs have decreased sedative effects. Still, because dogs and cats, like humans, can experience a huge range of effects when given a BZ, clients should be encouraged to give any BZ when they can monitor the patient. This practice is extremely helpful in ensuring that we recognize animals with atypical or serious sedative responses so that we can find more appropriate medications with which to treat them.

Most behavioral drugs are metabolized through renal and hepatic pathways so knowledge of baseline values is essential. That said, these medications can be used in compromised animals if adjustments are made and the animal is monitored behaviorally and biochemically.

All psychotropic medications can interact with other medications. For example, use of most anti-anxiety agents will cause thyroidal values, whether or not supplementation is involved, to read falsely low. Many of serotoninergic agents are thought to lower seizure thresholds and so are recommended with caution in patients treated with seizures. That said, there is now evidence in both the human and canine literature that anxiety may lower seizure thresholds and so treatment of the anxiety may allow the patient to successfully decrease the amount of seizure medication needed.

EFFICACY AND MECHANISM OF ACTION

It is important for clients to understand that newer, more specific, more efficacious drugs have a relatively long lag time between initiation of treatment and apparent changes in the patient's behavior. This delay is due to the mechanism of action of the tricyclic antidepressants (TCAs) and the selective serotonin re-uptake inhibitors (SSRIs), which employ second messenger systems to alter transcription of receptor proteins.

Serotonin

Serotonin (5-HT) receptors are all G-protein-coupled receptors. There are 14 identified classes of serotonin receptors. The 5-HT$_1$ receptors are linked to the inhibition of adenylate cyclase and affect mood and behavior. Presynaptic 5-HT$_{1A}$-receptors predominate in dorsal and median raphé nuclei; post-synaptic 5-HT$_{1A}$-receptors predominate in limbic regions (hippocampus and septum) and some cortical layers. Activation of pre-synaptic receptors by agonists results in decreased firing of serotonergic neurons leading to transient suppression of 5-HT synthesis and decreased 5-HT release; activation of post-synaptic receptors decreases firing of post-synaptic cells. These are 'thermostatic' effects, not integrated outcomes of receptor activation. The overall effect depends on regulation of second messengers (cAMP, Ca^{2+}, cGMP, IP_3) and their effects on protein kinases which then alter neuronal metabolism and receptor protein transcription.[5] The subclasses of 5-HT receptors vary in their affects. 5-HT_{1A} receptors affect mood and behavior. 5-HT_{1D} receptors affect cerebral blood vessels and appear to be involved in the development of migraine. These last two classes of receptor subtypes are the primary focus of many behavioral drugs. Urinary excretion of 5-HIAA (5-hydroxy indoleacetic acid) is a measure of 5-HT turnover and has been used to assess neurochemical abnormalities in human psychiatric patients, and has potential in this regard for veterinary behavioral medicine.

Nutraceuticals

Nutraceuticals designed to augment 5-HT or 5-HT supplements may not engender the same response as to pharmacologic agents because 5-HT does not pass easily through the blood–brain barrier (BBB), and instead requires the help of a transport protein. This transport protein is also used to move other amino acids across the BBB, and so, even if 5HT-containing substances are absorbed unchanged from the GI tract, they may be excreted depending on the pharmacodynamics of the other amino acids present.[6]

Noradrenaline/Norepinephrine (NE)

The most prominent collection of noradrenergic neurons is found in the *locus coeruleus* of the gray matter of the pons and in the lateral tegmental nuclei. There is also a cluster in the medulla. NE has been postulated to affect (1) mood [NE decreases in depression and increases in mania], (2) functional reward systems, and (3) arousal.

Dopamine

The distribution of dopamine in the brain is non-uniform, but is more restrictive than that of NE. Dopaminergic nuclei are found primarily in (1) the *substantia nigra pars compacta,* which projects to the striatum and is largely concerned with coordinated movement; (2) the ventral tegmental area, which projects to the frontal and cingulate cortex, *nucleus acumbens*, and other limbic structures; and (3) the arcuate nucleus of the hypothalamus, which projects to the pituitary. A large proportion of the brain's dopamine is found in the *corpus striatum*, the part of the extrapyramidal system concerned with coordinated movement.

Dopamine is metabolized by monamine oxidase (MAO) and catechol-O-methyl transferase (COMT) into dihydroxyphenyl acetic acid (DOPAC) and homovanillic acid (HVA). HVA is used as a peripheral index of central dopamine turnover in humans, but this use has been little explored in veterinary medicine. All dopaminergic receptors are G-protein-coupled transmembrane receptors. The D_1 receptors exhibit their post-synaptic inhibition in the limbic system and are affected in mood disorders and stereotypies. The D_2, D_3, and D_4 receptors are all affected in mood disorders and stereotypies. Excess dopamine, as produced by dopamine releasing agents (amphetamines and dopamine agonists, like apomorphine) is associated with the development of stereotypies. Because of this, and because acepromazine is a neuroleptic agent that scrambles memory but does not prevent or treat anxiety, ACEPROMAZINE SHOULD NEVER BE USED AS A BEHAVIORAL MEDICATION OR AS A TREATMENT FOR STORM PHOBIAS.

Gamma Amino Butyric Acid (GABA)

GABA, the inhibitory neurotransmitter found in short interneurons, is produced in large amounts only in the brain and serves as a neurotransmitter in ~30% of the synapses in the human CNS. The only long GABA-ergic tracts run to the cerebellum and striatum. GABA is formed from the excitatory amino acid (EEA) glutamate via glutamic acid decarboxylase (GAD), catalyzed by GABA-transaminase (GABA-T) and destroyed by transamination. There are two main groupings of GABA receptors: $GABA_A$ and $GABA_B$. $GABA_A$ receptors, ligand-gated ion channels, mediate post-synaptic inhibition by increasing Cl^- influx. Barbiturates and benzodiazepines are potentiators of $GABA_A$; however they do so by increasing the amount of time channels remain open - a relatively nonspecific change. It is for this reason why these are NOT suitable behavioral medications, and why one is more likely to get a sedated, rather than a less anxious dog, when the dog is treated with phenobarbital for behavioral reasons. $GABA_B$ receptors are involved in the fine-tuning of inhibitory synaptic transmission: presynaptic $GABA_B$ receptors inhibit neurotransmitter release via high voltage activated Ca^{++} channels; postsynaptic $GABA_B$ receptors decrease neuronal excitability by activating inwardly rectifying K^+ conductance underlying the late inhibitory post synaptic potential.

GABA also has a variety of tropic effects on developing brain cells. During ontogeny GABAergic axons move through areas where other neurotransmitter phenotypes are being produced, and so may be related to later monoaminergic imbalances. The extent such ontogenic effects are relevant for behavioral conditions is currently unknown but bears investigating.

EAAs (Glutamate, Aspartate, and, Possibly, Homocysteate)

EEAs have a role as central neurotransmitters and are produced in abnormal levels in aggressive, impulse, and schizophrenic disorders. The main fast excitatory transmitters in the CNS are EEAs. Glutamate, widely and uniformly distributed in the CNS, is involved in carbohydrate and nitrogen metabolism. It is stored in synaptic vesicles and released by Ca^{2+} dependent exocytosis, so calcium channel blockers may affect conditions associated with increased glutamate. Both barbiturates and progesterone suppress excitatory responses to glutamate. Pre-synaptic barbiturates inhibit calcium uptake and decrease synaptosomal release of neurotransmitters, including GABA and glutamate.

Roles for Neuronal Stimulation, Synaptic Plasticity, and Receptor Protein Transcription and Translation

What makes TCAs and SSRIs special and why are they so useful for anxiety disorders? The key to the success of these drugs is that they utilize the same second messenger systems and transcription pathways that are used to develop cellular memory or to "learn" something. This pathway involves cAMP, cytosolic response element binding protein (CREB), brain derived neurotrophic factor (BDNF), NMDA receptors, protein tyrosine kinases (PTK), particularly Src, which regulate activity of NMDA receptors and other ion channels and mediates the induction of LTP (long-term potentiation = synaptic plasticity) in the CA1 region of the hippocampus.

There are two phases of TCA and SSRI treatment: short-term effects and long-term effects. Short-term effects result in a synaptic increase of the relevant monoamine associated with re-uptake inhibition. The somatodendric autoreceptor of the pre-synaptic neuron decreases the firing rate of that cell as a thermostatic response. Regardless, there is increased saturation of the post-synaptic receptors resulting in stimulation of the α-adrenergic coupled cAMP system. cAMP leads to an increase in PTK as the first step in the long-term effects. PTK translocates into the nucleus of the post-synaptic cell where it increases CREB, which has been postulated to be the post-receptor target for these drugs. Increases in CREB lead to increases in BDNF and tyrosine kinases (eg, trkB) which then stimulate mRNA transcription of new receptor proteins. The altered conformation of the post-synaptic receptors renders serotonin stimulation and signal transduction more efficient.

Knowledge of the molecular basis for the action of these drugs can aid in choosing treatment protocols. For example, the pre-synaptic somatodendritic autoreceptor is blocked by pindolol (α-adrenoreceptor antagonist) so augmentation of TCA and SSRI treatment with pindolol can accelerate treatment onset. Long-term treatment, particularly with the more specific TCAs (eg, clomipramine) and SSRIs, employs the same pathway used in LTP to alter reception function and structure through transcriptional and translational alterations in receptor protein. This can be thought of as a form of in vivo "gene therapy" that works to augment neurotransmitter levels and production thereby making the neuron and the interactions between neurons more coordinated and efficient. In some patients short-term treatment appears to be sufficient to produce continued "normal" functioning of the neurotransmitter system. That there are some patients who require life-long treatment suggests that the effect of the drugs is reversible in some patients, further illustrating the underlying heterogeneity of the patient population considered to have the same diagnosis.

MONITORING

Monitoring of side effects is critical for any practitioner dispensing behavioral medication. The first tier of this involves the same tests mandated in the pre-medication physical and laboratory evaluation. Age-related changes in hepatic mass, function, blood flow, plasma drug binding, et cetera cause a decrease in clearance of some TCAs, so it is prudent to monitor hepatic and renal enzymes annually in younger animals, biannually in older, and always as warranted by clinical signs. Adjustment in drug dosages may be necessary with age.

It is generally preferable—but not necessarily required—to withdraw most patients from one class of drug before starting another. For most medications this is done so that one can be sure which medication is associated with any noted change in behavior. When changing between SSRIs and MAOIs a washout period is mandatory because of the potential for serotonin syndrom.......the recommended drug-free time in humans and dogs is two weeks (2 + half-lives: the general rule of thumb for withdrawal of any drug).

POLYPHARMACY

Oddly, because of the cytochrome systems that metabolize medication, it may be safer for the animal and more efficacious in terms improvement of the condition to combine medications. When medications are combined, knowledge of side effects and specific mechanisms of action is essential. That said, medications within related classes can usually be combined and such combination can allow a lower dose of each of the medications to be given. Medications of different classes can often be combined, if the potential side effects are compatible, and if the practitioner has a clear understanding of what conditions will or should respond to each medication.

For example, tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs) can be combined with each other, and, if needed, with other medication within the class. For this to be done rationally, however, understanding potentiation of effect and side effects is essential. TCAs generally exert their largest effects on serotonin (5-HT) receptors, norepinephrine (NE) receptors, and some histaminic receptors (H). Additionally, they can have effects on some of the adrenergic receptors. The latter is important primarily when premedication for anesthesia is involved. SSRIs primarily affect 5-HT receptors, and most have an affinity for the 5-HT1a subtype receptor. Additionally, there are some weak effects on NE receptors. TCAs that are less specific (eg, amitiptyline) and SSRIs that are more specific (eg, fluoxetine) will be the easiest to combine since the overlap effects on the receptor will be less, while the generalized sensitization of the receptors in the class will be augmented.

Combination treatment allows the clinician to use the lower end of the dosage for both compounds which minimizes side effects while maximizing efficacy. Furthermore, benzodiazepines can be used to blunt or prevent acute anxiety-related outbursts on an as needed basis in patients for whom daily treatment with a TCA or an SSRI is ongoing. Together, the combination of benzodiazepines and TCAs/SSRIs may hasten improvement and prevent acute anxiety-provoking stimuli from interfering with treatment of more regularly occurring anxieties.

When stopping a drug, weaning is preferred to stopping abruptly.[7] A model for how to do this is found below.[7] Weaning minimizes potential central withdrawal signs, including those associated with serotonin discontinuation syndrome[8,9] and allows determination of the lowest dosage that is still effective. If patients are withdrawn fully, rather than weaned from medication, they may not have the same response to the medication that they had originally. Patients with discontinuation or cessation syndrome become moody and lethargic, but these effects usually pass within a week. If they do not, re-assessment of the wisdom of stopping medication is warranted. Medications that have the longest $t_{1/2}$ of intermediate metabolites (eg, fluoxetine) are less likely to cause problems when withdrawn quickly than are those with short half-lives or no functional intermediate metabolites (eg, paroxetine). However, SSRIs that have the greatest in vivo reuptake capabilities (eg, paroxetine) may be more at risk for involvement in serotonin syndrome. Long-term treatment may be the rule with many of these medications and conditions, but maintenance may be at a considerably lower level of drug than was prescribed at the outset. The only way the practitioner will discover if this is so is to withdraw the medication slowly.

Because of these patterns, it is best NOT to withdraw animals from medication prior to anesthesia, but instead to adjust the pre-medication sedation so that fewer interactions, particularly of the adrenegic variety, can be expected.

Finally, many animals appear to stop responding to medication. Staying the course may be the best decision in some of these cases because the CPY system is an inducible one, and multiple medication changes may just make the animal more—not less—refractory.[10] Additionally, there is a huge range of genetic polymorphisms that determine how this system acts.[11] These are all poorly understood in dogs because they have been so little investigated. However, given their importance in human psychiatry we'd be remiss if we didn't start to believe that such patterns may no be independent of disease state.

Polypharmacy can be safe, rational, and cheap, and can save animals' lives. But this is an area that really requires an understanding of how these medications act. Fortunately, the functioning of these medications is easy to understand.

Sample Combinations[12]:

- amitriptyline (TCA) + fluoxetine (SSRI)
- amitriptyline (TCA) + fluoxetine (SSRI) + alprazolam (BZ)
- amitriptyline (TCA) [anxiety] + alprazolam (BZ) [panic]
- fluoxetine (SSRI) [anxiety] + alprazolam (BZ) [panic]
- clomipramine (TCA - relatively specific) [anxiety] + alprazolam (BZ) [panic]
- clomipramine (TCA - relatively specific) [anxiety] + diazepam (BZ) [panic / phobias] - could be pretty sedating
- amitriptyline (TCA) [anxiety] + diazepam (BZ) [panic/ phobias] - could be pretty sedating
- selegiline (MAO-I) (cognitive dysfunction) + diazepam (BZ) [panic / phobias]
- selegiline (MAO-I) (cognitive dysfunction) + alprazolam (BZ) [panic]
- paroxetine (SSRI) (social anxiety) + alprazolam (BZ) [panic / appetite stimulation in cats]

Table 1. Half-lives of Parent Compounds and Intermediate Metabolites of Target Benzodiazepines in Humans[7]

Parent Compound	$t_{1/2}$ Parent Compound	$t_{1/2}$ Intermediate Metabolite	Overall Duration of Action
Triazolam	2–4 h	2 h	Ultra short: 6 h
Oxazepam	8–12 h		Short: 12–18 h
Alprazolam	6–12 h	6 h	Medium: 24 h
Diazepam	24–40 h	60 h	Long: 24–48 h
Clonazepam	50 h		Long: 24–48 h

Table 2. Duration of Action of Parent Compound, Diazepam, and its Intermediate Metabolite, Nordiazepam (N-Desmethyl Diazepam), Which is Responsible for Most Sedation, in Selected Domestic Animals[7]

Species	Diazepam	N-desmethyl diazepam
Horse	24-48 h	51-120 h
Cat	5.5 h	21 h
Dog	3.2 h	3-6 h

Table 3. Relative Effects of TCA Parent Compounds and Intermediate Metabolites on NE and 5-HT re-uptake[7]

Parent Compound	Intermediate Metabolite	NE	5-HT
Desipramine		0	5
Imipramine	desipramine	+++	0
Amitriptyline	nortriptyline	0	0
Nortriptyline		0	0
Clomipramine	n-desmethyl clomipramine + clomipramine*	0	+++

* Does not include the specific effect of the intermediate metabolite as a selective serotonin reuptake inhibitor (SSRI)

Table 4. "Gestalt" of TCA and SSRI use based on $t_{1/2}$ of parent compounds and active intermediate metabolites, relative effects on NE and 5-HT, and extrapolations from multi-center human studies (7)

Diagnosis / Type of Condition	First Drug of Choice
Narcolepsy	Imipramine
Milder, relatively nonspecific anxieties	Amitriptyline
Milder, relatively nonspecific anxieties with avoidance of sedation	Nortriptyline
Social phobias / anxieties concerning social interaction	Paroxetine
Panic / generalized anxiety	Sertraline
Outburst aggression / related anxieties	Fluoxetine
Ritualistic behavior associated with anxiety, including OCD	Clomipramine

Table 5. Algorithm for Treatment Length and Weaning Schedule[7]

- Treat for as long as it takes to begin to assess effects:
  - 7–10 days for relatively non-specific TCAs
  - 3–5 weeks minimum for SSRIs and more specific TCAs

PLUS

- Treat until "well" and either have no signs associated with diagnosis or some low, consistent level:
  - Minimum of another 1–2 months

PLUS

- Treat for the amount of time it took you to attain the level discussed in (2) so that reliability of assessment is reasonably assured:
  - Minimum of another 1–2 months

PLUS

- Wean over the amount of time it took to get to (1) or more slowly. Remember, if receptor conformation reverts it may take 1+ months to notice the signs of this. While there are no acute side effects associated with sudden cessation of medication, a recidivistic event is a profound "side effect". Full-blown recidivistic events may not be responsive to re-initiated treatment with the same drug and, or the same dose:
  - 7–10 days for relatively non-specific TCAs
  - 3–5 weeks minimum for SSRIs and more specific TCAs

TOTAL: Treat for a minimum of 4–6 months

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HOW TO PET DOGS, HOW TO TEACH DOGS TO RELAX, AND WHY THIS MATTERS

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WHAT IS MEANT BY 'DEFERENCE' AND WHY IT IS IMPORTANT

Dogs have social systems that are very similar to those of humans. They live in extended family groups, they have extensive and extended parental care, will work as a group or a family to help care for the offspring, nurse their young prior to feeding them semi-solid, then solid, food, use play as one form of developing social skills, communicate extensively vocally and non-vocally, and—most importantly—dogs have a social system that is based on deference to others and that governs different roles in different contexts.

Fights for status or control are notoriously **rare** among wild canids, including wolves. Except in what humans perceive to be abnormal social conditions, most human social relations are structured by negotiation and deference to others, rather than by violence. Deference-structured hierarchies mean that the individual to whom others defer may differ depending on the contextual and social circumstances. Status is always relative and is characteristic that is conferred by members of the social group, not taken by force. Status is also not absolute. In the human situation, a child may defer to his parents' requests, but then be the leader on the playground to whom other children defer. Dogs are similar.

Much has been written about dogs viewing their human families as their packs. It's important to remember that "pack" is just a word to describe a canid social grouping, like "pod" described a group of whales, and "gaggle" describes a group of geese. The problem for our dogs is that there is a value judgment within the word. Humans have wrongly attributed a value structure and judgment to the word "pack" and then assumed dogs viewed us as part of theirs. While the pack comparison is not exact, dogs are social and generally will look to their people for guidance. Dogs often become problems when they cease to do this, or if they never do this, or if they cannot do this.

All social animals create some form of rule structure. While cats have very different social systems than do dogs and people, it's that rule structure that allows cats to respond to this program, as well as dogs, although it is primarily written for dogs. The rule structure is what allows all social animals to communicate with each other. Clear communication is essential in social animals because it avoids an inefficient and potentially dangerous use of time (eg, fighting). Because dogs are so similar to us in so many ways, and so frequently look like they are hanging on our every word, we assume that they are complying with **our** rule structure and all its nuances. Puppies actually need guidance in how to do comply with or negotiate our wishes, and problem dogs need to have a consistent, benign, kind rule structure explicitly spelled out for them: if the dog knows a consistent rule or behavior that will get the attention of their people, the dog will then be receptive to guidance. This is a form of discipline, but we need to note that people often confuse discipline and violence or abuse. Any use of any behavioral modification program must focus on relaxation and **MUST be executed without violence or physical abuse**, or you will earn your pet's distrust. In fact, for most dogs, withdrawal of attention is a far more profound correction than is physical abuse. Abused dogs or those consistently mismanaged with physical punishment will either learn to over-ride the punishment, or learn to seek it, since it may be the most common contact that they get.

Physical punishment includes leash or collar "corrections" using a 'choke' collar or a prong collar, hitting the dog, walking the dog into a pole or tree to make him pay attention, and tying the dog so that he cannot move. If these punishment techniques sound abusive, it's because most often they are. The true definition of punishment doesn't require pain: it requires a stimulus sufficiently powerful that the undesirable behavior is abandoned by the dog **with the subsequent result** that the probability of the dog exhibiting the behavior **in the future** is lowered. The emphasized parts of this sentence are important because unless these conditions are met the dog is not being 'punished'—they're being injured mentally and, perhaps, physically. By far, the more favorable way to handle undesirable behaviors—and we have to remember that we, as humans, have taste preferences that are different from those of dogs—is to prevent them. If they cannot or were not prevented, rather than punishing the dog we should ignore the behaviors and so withdraw any attention associated with them. Finally, we should be clear to the dog and tell the dog what behaviors **will** get the dog attention. It's utterly unfair to the dog to have him try to 'guess' what it is that will get you to stop yelling at him and start loving him, yet these are the circumstances to which many dogs are reduced. These three steps are what practicing deference is all about.

The intent of behavior modification using relaxation techniques is to set a baseline of good behavioral interaction between the client and dog, and to teach the dog that if he or she consistently is calm, quiet, attentive, and defers to his or her people, attention and rewards will follow. In turn, the people learn to have realistic expectations for their pet and to signal clearly, calmly, and kindly to their pet. This type of protocol also gives the clients permission to **not** be angry at the dog—instead, they can walk away. To have a great relationship with a dog it is not necessary to control the dog's every move. The best dog–human relationships are the ones where clear signaling is involved—and good play almost guarantees this—and ones where both dog's and human's needs are respected and met.

These goals are accomplished in a safe, kind, passive manner, and it is tougher to do this than clients frequently acknowledge. The reason for this is as follows: if the clients are talking, reading, or watching TV and the dog comes up to them and rubs, paws, or leans against them, the clients usually passively reach out and touch or pet the dog. The dog controlled that entire interaction. The traditional way to view this is to see it as a contest with the score as: dog, 1; human, 0. This competitive, confrontational approach to working with dogs injures our relationship with them and often ends with injuring the dog behaviorally or physically. In the example given, the dog controlled the interaction—with default 'permission' by the humans—and the dog learned that if he or she was persistent they could get attention, regardless of the form of the attention. However......something more important happened here. If the dog is uncertain, anxious, concerned, or worried about the rules of the interaction.......getting attention from the people in this context made all of those problems worse. Humans need to understand that they are **always** signaling to the dog whether they intend to or not and that dogs read non-verbal signaling better than people do. Given this, humans must assess if their response is rewarding the behavior that they think it is. Here's a hint: if the dog is getting peskier or more worried, the human is not reading the signaling situation correctly. This objective can be achieved by putting their butt on the ground for just a second and looking at the human.

THE ROLE FOR SITTING

Dogs naturally sit as part of their species-typical repertoire of deferential behavior. Sitting is a 'stop' signal that takes the dog out of the active interaction and allows him or her to focus on matters at hand. Dogs ask questions to get information, and sitting can be a form of asking a question. If you watch young puppies, they will back away from an interaction and sit at the periphery when they are uncertain. Their uncertainty is either addressed by observation, or because a dog detaches himself of herself from the group and approaches the puppy to provide the needed information. Sitting—a classic deferential behavior that all dogs understand—allows dogs to focus on their human and to communicate efficiently and accurately. Having the dog sit is not about "control" or "mastery" of the dog—it's about increasing the chance that you can signal clearly to the dog and that you have the dog's undivided attention while signaling. Because dogs naturally defer to other dogs by sitting or lying down and looking at them, we can have them defer to us and be ready to take their cues from our signals by having the dog sit.

The sit does not have to be and should not be prolonged at first. It can be as short as seconds as long as the dog's butt is on the ground and the dog is looking quietly at the person. Even a 5-week-old puppy can sit—butt flush to the ground for a few seconds—and look you, even if they are wiggle worms. Pups can even learn to sit and attend to the client (look at them for cues, make eye contact, look happy and attentive while being quiet) in exchange for a food treat. As soon as the puppy sits, the person should say "Good girl (boy)!" and give a tiny treat of something special. Simply as soon as the dog's butt is on the ground, praise the dog and tell him he is brilliant, and give the treat. Dogs can also be petted if and only if this will not arouse and distract them and cause them to rise.

Quite simply, the deferential behavior of sitting provides dogs with a rule that allows them to seek, and then take, guidance and help. **All** dogs should learn this and **no** dog is too old to learn this.

A few tips on how to look at a dog while communicating may be useful.

1. **Don't** "stare down" dogs. Normal dogs will look away, anyway, if you look scary enough, and troubled dogs will think you are a threat— because you are—and their anxiety or aggression will worse.
2. **Do** look at the dog or cat. Looking someone directly in the eye is the best way to ensure that you are communicating well. Looking at a dog is different than staring. When you stare you don't move your eyes, you stiffen the muscles in your face, and your pupils likely dilate. This is a threat. Looking is much more relaxed and is important for clear communication in all mammals with decent eyesight.
3. If when you just casually look at the dog or cat he begins to be aggressive, divert your gaze so that you can keep them in view with your peripheral vision, while not making direct eye contact. This will often lessen any aggression. It is always a horrible idea to try to "out-stare" any aggressive animal.

TEACHING RELAXATION

Any protocol designed to teach dogs to relax as part of a treatment program can also be used as a **preventative** program for puppies and kittens, dogs and cats. **The single biggest mistake vets and trainers make is to forget about the preventative use of these types of programs.**

Simply put, the purpose of this particular **Protocol for Relaxation** is to teach the dog or cat to sit and stay while relaxing in a variety of circumstances. The cat or dog cannot progress to learning how to relax unless he or she trusts the human enough to sit and attend to them when requested to do so.

It's the rare dog who will not sit and then look to another individual for instructions or information about what is to come next. *However*—and this is a **huge** *however*—dogs can sit and look at you, **and still be terrified**. If you reward the dog or cat when he or she is exhibiting any behavior other than a relaxed, calm pose, you have just inadvertently also rewarded their anxiety, fear, distress...whatever. This is **not** what you want to do.

Starting out — roles for spontaneous reward and using the 'shaping' technique: So, before you even start this program, learn what a relaxed facial and body expression in your pet looks like. Practice rewarding this expression. If you can only get the animal to look calm and relaxed for a few seconds at first, that's fine.....you can gradually expand the time they stay relaxed by rewarding the behavior every time it occurs and while it is continuing to occur.

Why do we wish to reward dogs only when they look progressively more relaxed? The amygdala is the region of the brain that is found at the anterior tip of the hippocampus. The main role of the hippocampus is to process associational learning. The main role of the amygdala is to regulate fear and to engender adaptive fear responses. These two regions are connected by a diffuse neuronal structure with projections to the frontal cortex. It should be clear how easy it is to reinforce and 'train' a fearful response given this organization. The frontal cortex, with the hippocampus, is the site of learning or—at the molecular level—long-term potentiation (LTP). Memories are stored via protein configuration changes that make new neurochemicals, new receptors, et cetera when these regions of the brain are stimulated over time. Consider how easy it would be to engender a fearful response that now becomes learned—with all of its associations—unless care is taken to avoid distressing the dog. Instead, we need to teach the dog that when he or she relaxes—when that relaxed and loose face appears, when he or she can take a deep breath—he or she will feel better. Dogs are cognitive, and can learn to learn, instead of learning to react, but they cannot do that without learning to relax first. Deep breathing and holding breath allows the dog to lower his or her heart rate and so diminishes the outward physical signs of arousal, diminution in pupil size indicates a physiological response to decreased arousal, and all of these add up to provide a learning situation that is not over-ridden by cortisol. We now believe that cortisol can act as a hormone response element (HRE). As such, it can block transcription of new proteins that would develop as part of learning. In short, very stressed and distressed dogs may comply with people's requests because of fear, but they cannot learn not to be fearful unless they can relax.

Often, because of endogenous factors or past experience it is difficult to get a 'relaxed look'. In such cases we should use successive approximation—reward a look that is less distressed. By using a learning technique called shaping you continually reward behaviors that are better approximations of the behavior you want. And.....**no shrieking at the dog or cat when they backslide**.......instead, you just ignore the anxious behaviors that are not going in the direction that you want (eg, more relaxed). For example, if—no matter what you do—the dog's eyes are popping out of his head and he's panting, just walk away and quit. This is **not** a contest or an endurance test. Then, when the dog spontaneously exhibits calm behaviors....maybe even before he goes to sleep..... reward **those** calm behaviors. Softly telling the pets that they are wonderful when they are already asleep is the least used trick to improve their behavior, but it works! Don't startle them, don't pet them, just quietly commend them.

For very, very anxious dogs, before you can even start a full relaxation program, you will have to spend a lot of time spontaneously rewarding the dog when he or she exhibits the relaxed behavior just in the context of everyday life. Only then, will that dog be able to move on to having their behaviors shaped in response to a request. After that, the dog can start the program, **but only after achieving an acceptable level of success where their calm behaviors are rewarded.**

Encourage clients to be gentle, but be consistent. Remind them that taking your anger or fear out on the dog will only make him or her worse. As soon as the dog responds and calmly sits, reward the dog, and continue. Never reward a dog that is growling, lunging, barking, shaking, or urinating.

Finally, please remember that the dog or cat will give you lots of cues about how they are feeling. Dogs are continually signaling information that people will find useful. In turn, they use human signals to adjust their own signaling and behavior. Dogs are cognitive and ask questions by offering behaviors. Take advantage of this and reward the most relaxed and informative behaviors. This program differs from other behavior modification programs because of the emphasis on these signals. We are rewarding the physical changes associated with relaxation and happiness and so will also reward the underlying physiological states associated with this (parasympathetic part of the autonomic nervous system). This means that if the dog is relaxed, his or her body is not stiff, his or her jaws hang relaxed and are not tense, his or her ears are alert or cocked, but not rigid, his or her head is held gently at an angle, and his or her eyes are calm and adoring, you will be rewarding the nervous system responses that help your dog to learn. If you mistakenly reward fear, tension, aggression, or avoidance, you will not make progress, and, over the long term, could do harm.

DEALING WITH AGGRESSION IN THE VETERINARY CLINIC

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Dealing with an aggressive dog or cat is not fun for anyone concerned. It is stressful for the owner, the dog or cat, as well as the target of the aggressive response. When it happens during a veterinary visit, it is even more difficult to deal with as we are seen as the professionals who should be able to handle with the situation. We are the ones who should be able to prevent the aggressive response. It is one of the most difficult situations to handle calmly. It can be a very confronting experience yet veterinary staff may face this in practice on a regular basis.

The way that the situation is handled at the time will impact on the way the visit is perceived by the dog or cat, the owner, and the staff. It will also determine whether the visit is traumatic or a potentially dangerous experience (not only for the dog or cat, but also for the staff). However, if handled well this visit can also be the first step towards making the next visit less stressful and more pleasant for all concerned.

After all, as the profession that cares for animals, the aim of all staff should be to make each visit, especially the first visit of the dog or cat to the veterinary hospital, as stress free and pleasant as possible.

Many years ago veterinarians had to rely on brute force and sheer numbers (ie, staff members) to manage aggressive animals. The animals were forcibly held down and the procedure was carried out. Not only did the veterinary profession not have quick-acting sedatives or anesthetics, we also did not have the behavioral knowledge we have today. In addition, the maxim was that it was important not to let the animal "win."

Today, however, we now have many more humane ways of dealing with difficult pets. We recognize that most of these pets are stressed or anxious and veterinary medicine has advanced so that we have many more ways of helping these pets. It should no longer be necessary to manhandle or wrestle any dog or forcibly restrain any cat. These days there is little need for a visit to the veterinary hospital to be a traumatic experience: not for the dog or cat, the owner, or the veterinary hospital staff.

In addition, concern for the animal's welfare should be paramount.

Veterinarians also need to recognize that most pet owners see their pets as family members. As such the owners of these pets find it very distressing to see a member of their family handled in such a forceful manner.

A much better result can be achieved by working with the animal and the owner. By recognizing why the animal may be behaving in such a manner each veterinary visit should become a more pleasant and less stressful experience for all concerned.

If adequate time is taken to observe the dog' s initial reaction to walking in the front door of the veterinary hospital, many unpleasant situations may be able to be avoided. Observation of the cat in its carrier can also provide valuable information on how best to proceed. Understanding and appreciating that the way an animal behaves is influenced not only by its genetic makeup and inherited predisposition but also its previous experiences (and what it has learned from them) we can try to make veterinary visits more pleasant for all. If we also appreciate that the current environment will also affect the way an animal behaves at a given time it is easy to see that by adapting our approach to each individual animal and each specific situation it should be possible to modify the pets 's reactions and response (behavior).

WHAT IS AGGRESSION?

Aggression can be defined as a threat, challenge or attack that is directed towards one or more individuals. It can be intra-specific or inter-specific. Aggression may be normal or abnormal depending on the context in which it occurs.

All animals can be aggressive. Aggression can be a normal behavioral response to a perceived threat or challenge. When faced with a fear provoking stimulus the flight, fight, or freeze response may be evoked. Aggression is a nonspecific sign, that is, it may be exhibited in many different situations. It may be passive (covert) or active (overt) and it is important to recognise that several different "categories" of aggression may occur concurrently. Pain is a common trigger for aggression.

The signs that are presented may be:

- visual (eg, changes in body posture, piloerection),
- auditory (eg, growling, hissing, spitting),
- olfactory (eg, spraying, scratching,) or
- tactile (scratching) and may involve use of teeth, claws, head

WHY DO THEY EXHIBIT AGGRESSION AT THE VETERINARY HOSPITAL?

The first step in recognizing why a dog or cat may be aggressive at the veterinary hospital is to look at the hospital from the animal's perspective. Start by assessing the sights, sounds, and smells from the animal's perspective. Many of the sights, sounds, and smells of a veterinary hospital that we take for granted can and do have a profound effect on our patients.

Try to walk in their paws! All dogs can bite. Some need less provocation than others. The main reason that dogs are aggressive in the veterinary clinic is they are anxious or fearful. It is very unlikely that they are being dominant as many assume.

Anxiety has been defined as the apprehension of future danger. The dog's response to anxiety provoking situations will be to fight, freeze, flee or "fiddle." Which response it uses will depend to some degree on what it has found successful in controlling the situation previously. Thus, if the dog has previously learned that snapping at the perceived threat has lead to it having some control over the situation, it is much more likely to react this way again next time.

Many dogs have also been taught that growling is an unacceptable behavior. Thus, the full behavioral sequence beginning with the warning is altered or truncated and the dog may resort to snapping or biting without giving a warning.

Cats can also exhibit aggression in a veterinary hospital situation. They may bite and scratch and inflict damage on the staff in the process. The reasons for aggression in a veterinary hospital can be many including fear, anxiety, and pain.

SO WHAT MAKES ANIMALS ANXIOUS OR FEARFUL?

Some dogs and cats are genetically more fearful or apprehensive than others. This is an important consideration and is not necessarily related to breed but rather lines of dogs or cats and may be a trait of the individual.

The senses of dogs and cats are also very different from ours. A dog's hearing is about four times more acute than ours, and they can hear ultrasound and infrasound, as can cats. Thus, dogs and cats can become sensitized to the noises in a veterinary clinic and this can make them apprehensive or reactive and more difficult to handle.

A dog's sense of smell is at least 1,000 times better than ours (some dogs can detect fingerprints on glass 6 weeks after they were placed there!). Cats are probably not dissimilar. Veterinary clinics have very distinct odors that can be disturbing to dogs and cats despite having easily cleaned surfaces that are not porous. Dogs and cats can also detect the pheromones that can communicate alarm or distress.

Dogs and cats are predators and as such are very good at detecting very slight movements. They can be easily startled by movement. Thus, sudden movements can also increase their apprehension and so animals need to be approached slowly and calmly to help make them more tractable.

Consideration also needs to be given to the surfaces that they stand or lie on. Many animals find it frightening to walk or stand on slippery surfaces. A dog that is already apprehensive may become even more reactive unless surfaces with secure footing can be provided to decrease anxiety and reactivity.

In addition, some of the medications used in a veterinary clinic can increase reactivity. For example, acepromazine increases noise sensitivity and may lead to more unpredictable behavior.

PREVENTION

A well run Puppy Preschool® or Kitten Kindy® class conducted at the veterinary hospital can provide a good introduction to the veterinary hospital; the outcome is having well-mannered dogs and cats in the veterinary hospital. These classes, run by experienced staff, allow the puppy or kitten, as well as the owner, to become familiar with the veterinary hospital in a non-threatening manner and associate it as a "friendly" place to visit.

MINIMIZING PROBLEMS

If the pet is already apprehensive about coming to the veterinary hospital the aim should be to make each subsequent visit less difficult than the current one. The attitude of the staff and the hospital environment can do much to help things run smoothly.

At all times, however, please remember you should not put your safety or that of others at risk!

So what can we do to make life easier for the pet, the veterinarian, the staff, and the owner?

TIPS FOR HANDLING AGGRESSIVE DOGS AND CATS

- SAFETY FIRST
- Walk in their paws – think of the world from their perspective
- TAKE YOUR TIME!
- ***DO NOT PUNISH!*** Physically punishing aggressive animals may make the situation worse, especially with frightened or anxious dogs and cats.
- Train young puppies and kittens to enjoy wearing a head collar and muzzle
- Have muzzles, head collars, towels ready in advance
- Ask the owner to muzzle the dog prior to coming to the clinic
- Initially ignore the dog and talk to the owner
- Never make direct eye contact with the dog or cat
- Watch your body language
- Approach quietly, calmly and slowly
- Whisper and breathe slowly
- Approach from the side, not from front or behind
- Offer treats
- Speak softly, calmly
- Slowly stroke (not pat) on the chest
- Don't use physical force
- ***Never*** use force or aggressive behaviours to deal with aggression.
- Use minimal restraint
- Use anxiolytics if necessary
- Do not be afraid of anaesthetizing animals
- DAP / Feliway
- Pre-medication **prior** to putting in the cage
- Use signs on cages to warn others eg (I Bite)
- Keep records on what works AND what does not to make it easier for all next time.
- Remember than an animal's behaviour will change day to day eg if in pain or not
- Put aggressive dogs on ground level cages to make it easier to get them in and out.
- Insulate metal cages with eg pink batts to decrease noise
- Use non-slip matting on examination tables to provide secure footing and decrease anxiety
- **Don't be afraid to walk away for another day!**

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KITTEN KINDY® AND PUPPY PRESCHOOL® – GOOD PRACTICE BUILDERS

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Our future depends on having pets that fit into our society. Therefore, it is our duty to help the pets in our community fit in to the society in which they are to live. Kitten and puppy socialization and training classes benefit not only the kitten or puppy and the owner, but also the veterinary hospital and the community. How to run them successfully and how to avoid future problems are key aspects of these classes. Properly run classes conducted at the veterinary hospital by veterinary staff will help build a veterinary practice that is respected in the community.

BACKGROUND

"Behave" is defined in the Macquarie dictionary as "to act in a socially acceptable manner." Thus, the idea behind running kitten and puppy socialization and training classes is to help our pets become more socially acceptable to their owners as well as the community.

Behavior is influenced by three main factors. These are:

- An animal's genetically inherited tendencies or predisposition to exhibit a particular behavior
- The animal's previous experience and what it has learned
- The particular environment at the time, including the motivation at the time

It is also important to distinguish between "problem behaviors" and "behavior problems." When people talk about an animal's problem behaviour, it is when the pet does not behave as they wish, it is usually a normal behavior but socially unacceptable to the owners. However, some animals exhibit abnormal behaviors and these need to be identified and managed very differently.

PET OWNERSHIP

The reason that people decide to own a pet will influence how they perceive their pet. For example, if they see their pet as a companion rather than an "item" needed to indulge their sport or giving them prestige or security, the way they interact with the pet will vary.

Many studies have suggested that there are health benefits of owning pets, such as a reduction in stress, blood pressure, and serum triglyceride levels, but this is unlikely to be the reason for people deciding to own a pet.

Although there are many benefits of pet dog ownership, there are also known to be problems as evidenced by the number of dogs that are surrendered to pounds each year. This would seem to indicate that dogs exhibit behaviors which lead to a disruption of the human–companion animal bond. Each year about 20% of urban dogs are surrendered to pounds and animal shelters and of these, 80% are euthanized. Surveys indicated that up to 80% of these dogs were surrendered because of behavior problems.

The largest cause of death of pets is said to be euthanasia due to behavioral problems. Most dogs and cats do not live to their full age potential, with the average age of dogs estimated to be only 3.5 years while for cats it is 5.6 years.

There are many factors that appear to increase the risk of pets being euthanized or abandoned. Incorrect choice of pet, unrealistic expectations of the pet, and an undervaluing or perhaps, and ignorance of the time, money and effort required to be a *socially* responsible pet owner all contribute to the problem. The large numbers of dogs and cats surrendered worldwide is a tremendous financial and emotional burden to the people and organizations involved in dealing with the problem. Interventions that might reduce the likelihood of euthanasia or abandonment of pets, such as Puppy Preschool® and Kitten Kindy®, should help reduce these problems.

The reported prevalence of problem behaviors or behavior problems ranges from 42% to 87%. The most common problems, apart from aggression, that owners report to veterinarians and dog trainers include such behaviors as digging, jumping up, barking, destructiveness, and chewing. The most common problems in cats are elimination problems and aggression to other cats and to people. These all form part of an animal's normal behavioral repertoire. Although many feel it is important to "stop" these behaviors It is possibly detrimental to the animal's welfare to try to stop them entirely. That is not to say, however, that they cannot be modified to a more socially acceptable behavior by altering the time, place, or duration of the behavior.

To be successful in trying to change the occurrence of these behaviours, it is essential that the owner understands why the pet may be behaving in this way and how to respond accordingly. A little basic understanding of the nature of dogs and cats and their needs can be very helpful in dealing with the problem. *This is one of the important reasons for running Puppy Preschool® and Kitten Kindy® classes.*

In general, confinement and lack of activity may often exacerbate some of these unacceptable, destructive and nuisance behaviors. Dogs and cats are highly intelligent, active, social animals that need activity, company and stimulation (both physical and mental!).

Counselling owners about the most suitable pet for their particular circumstances BEFORE they actually acquire a pet would be the ideal situation. This is a service that many of us can offer but few do so at present. Offering advice on choosing a pet based not only on owner lifestyle, owner expectations and personal preferences as well as their dog's innate characteristics may help owners deal better with the behavior and make their expectations of the dog or cat more realistic.

WHAT IS SOCIALIZATION?

Socialization is defined as a special learning process where an animal learns to accept the close proximity of members of its own species as well as that of other species. Therefore, animals that are well socialized will be able to live in harmony with others.

WHAT ARE PUPPY SOCIALIZATION AND TRAINING CLASSES (PUPPY PRESCHOOL®)?

Puppy Preschool® is specifically designed for puppies 8 to 14 weeks of age to help them become sociable and manageable pets. They are NOT obedience classes for younger dogs.

Puppy Preschool® aims to help prevent behavior problems, educate owners on all aspects of raising a puppy and then living with a dog in the family, as well as establish a close bond between the puppy, the owner, and the veterinary hospital if that is where they are conducted. Training puppies has to be fun as well as appropriate, not only for the puppy but also for the whole family.

Why Do We Need Puppy Preschool®?

Being a puppy is one of the most important stages in a dog's life. This is the vital age to start training and socialising the puppy as everything the puppy sees and experiences will have a great effect on how he behaves as an adult.

As is well recognized, puppies have a sensitive period of development called the socialization period that occurs from about 3 weeks to 3 months of age and any experiences the puppy has during this time can affect later behavior. From many early studies it is now known that dogs that have been isolated during this time are more likely to be hyperactive, aggressive, difficult to train, antisocial, and fearful.

To develop into normal, friendly and confident adults, puppies need to be regularly handled and to be exposed to many new and novel situations in a non-threatening way. Puppies that are not exposed to other dogs during the socialization period are more likely to develop aggressive or fearful responses to other dogs later, just as puppies that are not socialised to humans often develop behavioral problems. Unfortunately many puppies are not homed until after this age or go to homes where they may not experience a wide variety of situations.

They also need to interact with dogs of various breeds if they are to be well-behaved members of our community. Starting puppies off the right paw is much easier (ie, teaching the puppy the correct and socially acceptable behavior) than trying to correct bad behaviors later, when the puppy has had 6 months or more to learn them. Puppy Preschools® are a safe way of helping a puppy to be well socialized and start with the basics of training.

Dog owners also need to be educated and taught how to look after and to train their pets to become suitable members of the community. Most dogs are kept as companion animals and it is for this reason that puppy training classes are an essential part of teaching owners how to teach their puppies basic good manners rather than traditional obedience type exercises.

KITTEN SOCIALIZATION AND TRAINING: KITTEN KINDY®

Although the advantages of puppy training are now well established and accepted, many people still do not appreciate that kittens would also benefit from such classes that focus on early handling and training. Cats require socialization with members of their own species as well as humans and dogs if they are to become social members of the household. Studies have shown that early handling of kittens in a gentle, non-threatening manner is just as important for cats as dogs for their normal development.

Kitten Kindy® is an early socialization, training, and education program designed to help owners and kittens start off on the right track together. The goal of Kitten Kindy® is to help prevent behavioral problems, educate owners on all aspects of raising a kitten, and then live with a cat in the family. They aim to establish a close bond between the cat, the owner and the veterinary practice.

Kitten Kindies® are ideal for kittens under 12 weeks of age to help them develop into manageable and social adult cats. Because of the socialization period of cats kittens should be no more than 14 weeks old when they finish the classes. Kittens more than 14 weeks old may be more likely to fight rather than socialize with the other kittens. The classes allow kittens to explore new environments, learn to play with other kittens, play with toys and develop confidence in new surroundings. Ideally, the younger the kitten the better for maximal socialization. Hand-raised kittens or kittens from small litters appear to benefit especially from these social interactions.

The classes should also aim to teach owners about normal feline behavior as well as how to play and interact appropriately with their kittens. The focus should also be on teaching owners on how to prevent problems behaviors as well as on other preventative medicine issues.

PLANNING CLASSES

For maximum benefit the classes should be are held at your Veterinary Hospital. This way the pets and their owners meet you and your staff and become familiar with the hospital. However, these classes need careful planning. The outcome of the classes should be considered in advance. This should include the aims and outcomes.

The classes need to be fun, as well as providing a relaxed and safe environment for learning both pets and owners. They should be run by the *most* experienced trainers that are familiar with learning theory and canine/feline behavior.

The classes should aim:

- To educate owners on *socially* responsible pet ownership
- To inform owners about normal canine/feline

behavior
- To explain to owners how to train their puppy/kitten at home
- To allow puppies/kittens to socialize in a safe and controlled situation
- To teach puppies/kittens to accept gentle handling from humans
- To teach puppies/kittens manners
- To teach puppies/kittens to be calm on cue
- To provide solutions to common issues such as housetraining, biting, scratching, jumping, chewing
- To encourage ongoing training for dogs
- To help owners to have realistic expectations of their pets
- To build a strong bond with the practice

Benefits
- Better behaved adult pets
- Better educated owners
- Better educated veterinary staff
- Increased self esteem for staff
- Increased practice profits
- Increased client visits

USEFUL REFERENCES AND FURTHER READING

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UNDERSTANDING LEARNING THEORY – WHY IT'S IMPORTANT

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Behavior is controlled by its consequences. If the consequence is "good" then the behavior is likely to be repeated, and conversely, if the consequence is "bad" the behavior is unlikely to be repeated. This is one of the key concepts that needs to be understood when dealing with animals.

LEARNING THEORY

The two principles of learning that are commonly used when discussing how to modify the behavior of dogs and cats are classical and operant conditioning. Classical conditioning, also known as Pavlovian conditioning, was first studied by Pavlov in the early part of the last century. Conditioning is said to have occurred when the repeated pairing of a neutral stimulus (Conditioned Stimulus, CS) with a biologically significant event (an unconditioned stimulus, UCS), results in the production of a response (Conditioned response, CR) when the CS is presented alone For example, the words "good dog" are initially neutral—that is, these words mean nothing to the dog. However, they may become a CS via Pavlovian conditioning by being paired with biologically significant events such as presentation of a food treat or a pat on the head. The conditioned response in this example is likely to be tail wagging.

Operant conditioning, or instrumental learning, is the primary method in which dog training is achieved. Operant conditioning teaches the animal to perform a voluntary response in order to obtain a reward. Presentation of a positive reinforcement or reward, such as food, increases the chances of a particular response being repeated Hence, the dog learns that behavior is controlled by its consequences. Similarly, an animal will perform a behavior to obtain secondary rewards, or stimuli, consistently presented with the primary reinforcer (for example, for the words "good dog" which were paired with food presentation).

The likelihood of a particular behavior being repeated depends on the nature of the consequences. Thus, if the consequence is pleasurable, such as a piece of food or a game, then the behavior is more likely to be repeated. Using this methodology new behaviors can be shaped in the animals. For example, behaviors such as "sit" or "stay" can be taught to be expressed in response to a verbal and, or visual cue.

DEFINITIONS

Reinforcement - Increases the chances that behavior will recur.

Positive Reinforcement - This is a reward (something pleasurable) that, when given immediately after a response, **increases** the probability of that same behavioral response occurring again. For example, if a dog is rewarded for sitting by being given a tasty piece of food after being given the cue "sit," then the dog is more likely to sit next time that same verbal cue is given.

To be most effective the reward has to be:

- Immediate
- Consistent
- Desirable

Negative Reinforcement - This is often confused with punishment. It is something unpleasant or aversive that, when it is removed immediately after a response, **increases** the probability of that response recurring. For example, loosening the choke chain after a dog stops pulling on it teaches the dog that it is less painful to walk to heel than to pull on the lead.

Punishment - Decreases the chances of the behaviour recurring.

Positive Punishment - It **decreases** the probability of the preceding response occurring again. Positive punishment is the addition of an aversive stimulus or event. For example, yelling at the dog or smacking would be considered a punishment if it lead to a decrease in the behavior.

To be most effective the reprimand needs to be

- Immediate
- Consistent
- Sufficiently aversive

Negative Punishment - The withdrawal of a pleasant stimulus or event that leads to a decrease in a behavior is considered a negative punishment. For example, placing a dog into a "sin bin" immediately after performing an unacceptable behavior would be considered a negative punishment if it leads to a decrease in that behavior.

Timing - The timing is crucial with both reinforcement and punishment. The time between the response and the punishment or reinforcement must be immediate, less than 1/2 second for the animal to make an association. By reinforcing 5 seconds after the response the learning time, ie the time for the animal to make an association may double.

In summary, reinforcement increases the probability of a response; punishment decreases the probability of response.

MODIFYING BEHAVIOUR

Training essentially means teaching animals what we want them to learn. Most training involves the use of operant conditioning. It is very effective as there is "something in it" for the animal. However, classical conditioning is also very important and often overlooked.

Learning is fastest when the reward is given immediately after the desired response (preferably within ½ second), very desirable and given every time the response occurs.

A continuous reinforcement schedule (when rewards are given every time a response is made) is used to teach a response, but does not help maintain the response. When the rewards cease, often so does the behavior.

A better way to ensure continued performance is to use what is called a variable reinforcement ratio. This may mean rewarding at set intervals, perhaps every third or fourth response. However, it is important not to introduce this until the desired response is learned. Once a response is learned it will become very difficult to extinguish if the rewards are then given intermittently. The poker machine (slot machine) is a great example of its effectiveness in people.

Punishment is the least effective way of changing a behavior, yet it is the technique that generally animals (and people) experience the most. Just think about how often the word "no" is said to the average dog in its lifetime? And think about how often it is effective.

Punishment is not reliable when trying to modifying behavior because it does not teach what behavior is actually expected in the circumstances—that is, it does not lead to an alternative response.

In addition, despite what the name may infer punishment does not have to be **painful** and it does not necessarily mean physical punishment. Punishment may also impede learning as it may increase anxiety. Repeated use of punishment decreases its effectiveness. Think about how often you have said, "If I've told you once, I've told you a thousand times not to ...." Generally, a good rule of thumb is if the same punishment has to be administered more than three times it means that the principles are not being followed and it is unlikely going to be effective.

In practice it is very difficult to effectively administer punishment and it is easier and more useful to teach the desired response instead.

MODIFICATION OF BEHAVIOR IN PRACTICE

When animals exhibit unacceptable behaviors, there are many issues that need to be considered when trying to change these behaviors.

- A behavior modification program is likely to be more successful if the following are addressed.
- The client understands the underlying cause(s) of the behavior.
- The client understands the basic principles of learning theory.
- The client understands the pet's motivation to perform the behaviors.
- The client has realistic expectations—no pet will ever be perfect even if it appears that their last pet was!
- Some behaviors are not changeable or modifiable.
- Behavior modification takes time and patience. It is not an overnight quick fix so setting realistic time frames in which to expect changes should be addressed.
- The client recognizes that they will have to maintain the behavior modification program for the life of the pet.
- The client appreciates that a consistent approach is needed.
- To be effective any behavior management program needs the full commitment of not only the owner, but also the owner's family. Everyone who is in regular contact with the pet needs to be consistent in their interactions with the pet. If someone cannot or will not follow the protocols it is better that they ignore the animal instead of interacting with the animal.
- Regular recheck appointments and follow-up phone calls are scheduled.
- The training is realistic with regard to time commitment and level of complexity.
- The training is fun for both client and pet.

Factors that may decrease the likelihood of success include:

- The client has unrealistic expectations of the pet. Not all dogs can or will be Lassie!
- The client has unrealistic expectations of what can be achieved and in what time frame.
- The client is unaware that as a behavior management program is instigated the pet may actually get worse before it gets better. As the owners start to alter the way they interact with the pet it may take some time for the pet to adjust to the new routine.
- Unanticipated or even unexpected responses occur. These need to be worked through step by step with the owner and possible reasons explained.
- The program is too involved or complicated, too time consuming or too difficult.
- There is disagreement between the owners as to what the problem actually is, the severity of the problem, etc.
- The motivation to persist with the behavior modification program decreases over time so that the problem behaviors reappear.
- The client feels that no ongoing support is available.

Points to Remember

- Animals go on learning whether we intend to teach them to or not.
- They learn by watching us.
- They learn by watching conspecifics.
- They learn fastest when they are rewarded every time.
- They learn fastest when the reward is very desirable.
- We can shape an animal's behavior by repeatedly rewarding behaviors that successively become closer to the one we want.
- A behavior can become extinct if it is ignored (not rewarded).
- Behaviors that have been intermittently rewarded take the longest to become extinct.

Ten Top Tips

- As behavior is determined by its consequences make each consequence good
- Reward acceptable behaviors, ignore unacceptable behaviors
- Reward immediately
- Use desirable rewards
- Reward intermittently once the behavior is learned
- Be patient
- Avoid punishment
- Teach good manners
- Motivation is important
- Have fun!

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HEAD COLLARS – DIFFERENT TYPES, HOW THEY WORK AND HOW TO FIT THEM

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WHAT ARE HEAD COLLARS?

Head collars are a training tool. They are a piece of equipment that fits on the dog's head much like a halter fits on a horse or cow. There are many designs and brands available for dogs.

The general principle of all head collars is a strap that fits around the dog's neck and another strap that sits across the dog's nose (muzzle). In most cases the lead attaches under the dog's chin and there may be a "connector" that acts as a safety device that attaches to the dog's regular collar. There are some head collars where the lead attaches at the back of the dog's neck.

WHY USE HEAD COLLARS?

Head collars are used to help teach dogs to walk on a loose lead (ie, without pulling). They are useful to help the dog focus on the owner and break the dog's attention on other dogs or people. They are commonly recommended for many behavior problems. They can also be used to help during a veterinary examination. They appear to have a calming effect on some dogs.

WHICH IS THE BEST HEAD COLLAR AND HOW TO CHOOSE ONE?

The best head collar is the one that fits the dog the best. The choice of head collar will depend on the shape of the dog's head and the length of the dog's nose. Color, style, and owner preference also play a part in deciding which head collar is used. The previous experience of the head collar fitter with various types will also affect choice.

Some dogs appear to more easily accept collars where the leash attaches behind the neck better while other dogs better accept head collars where the leash that attaches under the chin.

TEACHING DOGS TO ACCEPT A HEAD COLLAR

All head collars should be fitted properly by someone who knows how to do so. This may take up to 20 minutes to achieve. The neck strap should fit high and tight on the neck. It should be snug (like a watch strap fits on the wrist). The nose loop should be tight enough so that the dog cannot get it off but loose enough so that the dog can still open its mouth and pant. If pulled towards the nares it should not be able to be pulled over the nose.

It is a good idea to let the dog get used to the pressure of head collar before the leash is attached. A very light leash (such as a cat leash) should be the first one used to accustom the dog to the added pressure. It may take several weeks for some dogs to accept wearing a head collar.

It is important for the dog to get used to accepting the light pressure of the nose loop on the muzzle in stages. Start by rewarding the dog, with small pieces of tasty treats, when it sits. Then reward when the dog puts its nose near the nose loop. Then encourage the dog to put its nose through the nose loop. Always reward immediately.

The more the dog practises putting its nose through the nose loop before moving to tightening the neck strap the better.

Once the dog seems happy putting its nose through the nose loop, slowly increase the time the nose loop rests on the dog's nose. Over time, with rewards, the dog should look forward to putting its nose through the nose loop.

Only then start doing up the neck piece. Give the dog treats at each step. When the dog accepts wearing the head collar it is a good idea to let the dog wear it for variable periods of time around the home. Eating with the head collar will let the dog associate the head collar with positive experience. The head collar should not be taken off at any stage if the dog scratches or paws at it (unless the dog is really distressed). If the dog fusses at the head collar the dog should be distracted and asked to sit and focus on the owner. It should be rewarded when it does. Only once the dog is relaxed should the head collar be removed.

THE DOG ACCEPTS THE HEAD COLLAR – WHAT NEXT?

Attach the lead and practice at home. If the dog pulls then the owner should stop moving. When the lead is loose then can the owner move forward again. If the lead tightens then the owner should stop moving forward and start again only when the lead loosens.

THE DOG IS NOT HAPPY WITH THE HEAD COLLAR – WHAT NEXT?

The major problems are:

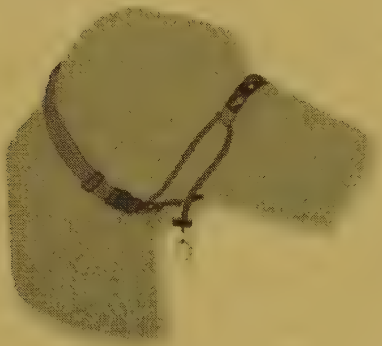
- Insufficient time to get used to the head collar
- Neck strap not snug enough
- Inaccurate fitting of head collar
- Incorrect choice of size/ type of head collar
- Taking head collar off when the dog is fussing

Loosening the neck strap means that the head collar is more uncomfortable for the dog as it will rotate more.

DIFFERENT TYPES OF HEAD COLLAR

There are several types of head collar available; some of these are shown in Figure 1. Each collar fits slightly differently. Consult the relevant Web site for each collar for detailed step by step instructions on their use.

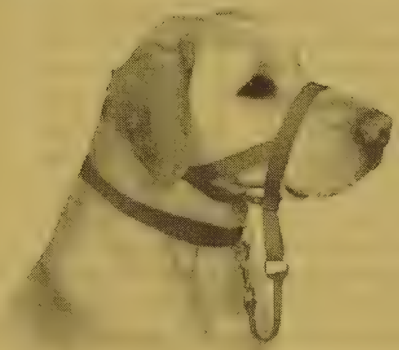
Black Dog



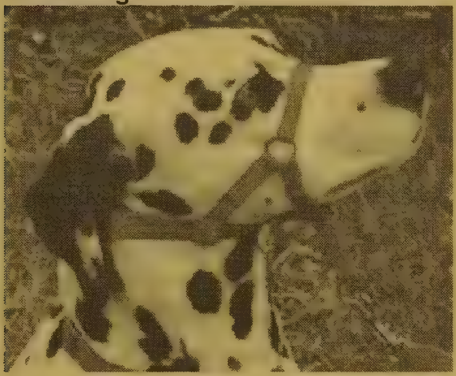
Canny Collar

Gentle Leader

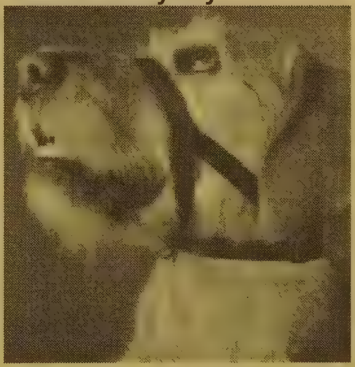
Halti



Kumalong



NewTrix Easyway



Snoot Loop

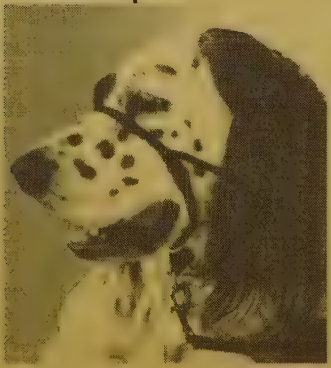


Figure 1. Examples of types of head collars for dogs.

MUZZLE TRAINING

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MUZZLES

Muzzles are one of the tools veterinary staff can use to minimize the chances of injury when examining aggressive or reactive dogs.

Ideally muzzles should be introduced to dogs when there is no need for them. This can be done in a Puppy Preschool® class or at the puppy's first visit. It can also be done by owners of the more reactive dogs at home to help keep veterinary office staff safe.

There are several types of muzzle commercially available. Custom made muzzles are also available for dogs. This is especially useful for brachycephalic breeds and those dogs with broad or large muzzles.

Regardless of the type of muzzle, it should not cause distress to the dog; it should allow the dog to pant and the owner to give treats for relaxed or appropriate behavior. A basket-style muzzle (either plastic or leather) is usually the best choice as it allows dogs to pant and drink water if needed. Therefore, they can be used for extended periods as well as when the dog is exercising.

Many dogs that are anxious bite. A common sign of anxiety is panting, so in order to decrease or at least not increase the dog's anxiety the muzzle should allow the dog to pant comfortably. For this reason, basket-type muzzles tend to be the best option for dogs that are anxious, exercising, or wearing the muzzle for any time periods more than a few minutes. Even in the short term, the ability to pant means that stressed dogs are less anxious.

WHY USE MUZZLES

Apart from being important for the safety of staff when examining reactive dogs, there are many reasons to use muzzles. Muzzles help owners of aggressive dogs to relax and also act as a warning to approaching dogs and people that the dog is reactive. This can be very useful for reactive and aggressive dogs.

Muzzles will reduce the risk of bite injuries. However, they are not an absolute guarantee in this regard as muzzles can break or come off and dogs can still do damage by bowling other individuals over and causing bruising.

FITTING A MUZZLE

If the dog is introduced to the muzzle gradually, then most dogs will accept it very readily. It is important to first encourage the dog to approach the muzzle and offer a treat. Once the dog readily approaches the muzzle then it is possible proceed to the next step. Fitting a muzzle may take a considerable period of time and requires patience.

Start by placing a tasty piece of food on the strap end of the muzzle and allow the dog to eat it. Over a few repetitions it will be possible to place food treats further into the muzzle itself so that the dog puts its muzzle further into the basket. It takes time for a dog to get used to having his muzzle in an enclosed space so do not proceed too quickly. Smearing sticky food such as peanut butter into the bottom of the muzzle will increase the length of time the dog spends with its nose in the enclosed area of the muzzle. Only when the dog is relaxed should there be any attempt to do up the neck strap, even momentarily.

As the dog accepts putting his nose into the muzzle slowly progress to having the dog wear the muzzle for more than a few seconds. If the dog is relaxed and does not attempt to remove the muzzle or fuss at it then proceed to keeping the muzzle on the dog for progressively longer periods, say a minute, then two, and so on.

The dog should always have a positive association with wearing the muzzle. Pairing wearing the muzzle with good things, such as walks, meals, or attention will help the dog accept the muzzle more quickly. Indeed many dogs actually look forward to wearing the muzzle at it brings rewards.

Some muzzles will need a little modification to allow food treats to be given easily. Treats such as vegemite, peanut butter, pâté, and cream cheese can all be applied to the end of the muzzle as an added incentive to want to keep it on, too.

Even when the dog is comfortable wearing the muzzle, it is important for the dog to be rewarded periodically with food when the dog is wearing it so that the dog continues to associate the muzzle with pleasant experiences.

DIAGNOSIS AND TREATMENT OF PERICARDIAL EFFUSION

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Pericardial effusion is defined as the accumulation of fluid within the pericardial space. As the pressure within the pericardial space increases, right-sided cardiac filling is impaired, resulting in decreased stroke volume with subsequent decreases in cardiac output and ultimately decreased oxygen delivery to the tissues (shock). These manifestations of pericardial effusion are referred to as cardiac tamponade.

TRIAGE AND PHYSICAL EXAMINATION

The most common presenting complaints from the owners of dogs with pericardial effusion and cardiac tamponade are lethargy, anorexia, collapse or syncope, abdominal distention, and dyspnea. Vomiting also appears to be a somewhat common complaint additionally. Major body systems assessment of the dog with pericardial effusion will likely reveal compromise to one or all of the major body systems (cardiovascular, respiratory, and CNS).

Upon identification of compromise to the major body systems, the patient should be moved to the treatment area for further assessment including full physical examination, measurement of blood pressure, oxygen saturation, cardiac rhythm (ECG), and placement of an intravenous catheter from which a small blood sample for packed cell volume (PCV), total solids (TS), blood glucose +/- venous blood gas and electrolytes + lactate can be rapidly acquired. If possible, blood for complete blood count (CBC), serum biochemical profile, and coagulation profile or activated clotting time (ACT) should also be collected. Concurrently, a second team member will be able to collect a full medical history.

Physical examination should still be centered on the major body systems, but subtle findings supportive of pericardial effusion may be noted including:

- Jugular venous distention +/- jugular pulses: due to right sided congestive heart failure.
- Muffled heart sounds/normal lung sounds
- Abdominal distention: ascites and hepatic engorgement may result from longstanding (days) pericardial effusion/cardiac tamponade due to right-sided congestive heart failure. Abdominocentesis will frequently reveal a relatively clear fluid will low cellularity and a protein concentration greater than 2.5 g/dL but less than 3.5 g/dL most consistent with a modified transudate.
- Pulsus paradoxus: An inspiratory fall of arterial systolic blood pressure of more than 10 mmHg resulting in variation in pulse intensity with respiratory cycle due to increased venous return during inspiration, increased right-sided filling, shifting of the interventricular septum to the left with decreased left-sided diastolic filling and subsequent decreased left-sided stroke volume. Pericardial effusion causing cardiac tamponade should be HIGHLY suspected based on signalment, history, and physical examination findings, supported by diagnostic testing such as abdominocentesis and electrocardiography (+/- radiography) and confirmed through point of care diagnostic imaging techniques (echocardiography).

DIAGNOSTIC TECHNIQUES

Electrocardiography

Assessment of ECG in patients with pericardial effusion may reveal sinus tachycardia +/- ventricular arrhythmias. Ventricular arrhythmias may result from decreased myocardial oxygen delivery or aberrant conduction associated with the underlying cause of the effusion. QRS complexes <1 mV in amplitude and the presence of electrical alternans (regular or irregular variation in QRS complex amplitude associated with the heart moving within the pericardium to and from the positive pole of lead II) are supportive of pericardial effusion.

Echocardiography

Echocardiography is the diagnostic test of choice for rapid, stress-free confirmation of the presence of pericardial effusion in the dog. Many dogs with pericardial effusion have SEVERE cardiovascular compromise and can be on the verge of death. The stresses associated with radiographic imaging may put cause these patients to decompensate. Echocardiographically, pericardial effusion appears as a hypoechoic space located between the hyperechoic pericardium and the right ventricular wall when viewed through the right cardiac notch (Figure 1). The presence of pericardial effusion provides excellent contrast to aid in the diagnosis of cardiac masses; however, pericardiocentesis should NOT be delayed in a patient with signs of shock simply to aid the diagnosis.

Thoracic Radiography

As previously mentioned, thoracic radiography can be an extremely stressful procedure for dogs with cardiac tamponade. However, not all practices are equipped with ultrasound capabilities. If thoracic radiography is performed in dogs with suspected pericardial effusion, ventrodorsal positioning should be avoided in favor of dorsoventral positioning. Lateral thoracic radiographs may also be performed. Supportive radiographic findings include an enlarged, globoid cardiac silhouette. Acute effusions may not cause severe enlargement of the cardiac silhouette because the pericardium has not had time to enlarge. Concurrent pleural effusion may be present. The other primary differential for a globoid heart is dilated cardiomyopathy (DCM) or other underlying cardiac disease. Key findings to try to differentiate DCM from pericardial effusion include:

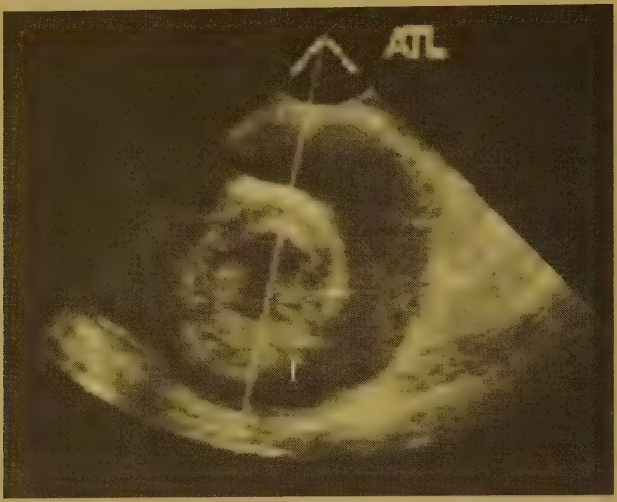

Figure 1. Echocardiogram from a dog with pericardial effusion. Note the hypoechoic fluid (f) surrounding the left ventricle (v).

- **Heart sounds:** Heart sounds in dogs with DCM are frequently normal in contrast to the decreased heart sounds seen in pericardial effusion. A systolic murmur may be noted in dogs with DCM and is uncommon in dogs with pericardial effusion.
- **ECG:** Atrial fibrillation is common in dogs with DCM. Atrial fibrillation is uncommon in dogs with pericardial effusion. Electrical alternans may be seen in dogs with pericardial effusion.
- **Cardiac Silhouette:** The silhouette of the heart on thoracic radiographs of dogs with pericardial effusion tends to be extremely round with sharp borders. The silhouette of the heart in dogs with cardiomyopathy can be round, but often, there are still some dimples or "waist" associated with the divisions between the chambers and the borders of the cardiac silhouette tend not to be as sharp because of motion artifact.
- **Pulmonary infiltrate:** Pulmonary edema is common in DCM and uncommon in pericardial effusion.
- **Pulsus paradoxus:** Common in pericardial effusion, uncommon in DCM.

ETIOLOGY

Pericardial fluid accumulation and cardiac tamponade in the dog most often occurs secondary to a neoplastic process. Hemangiosarcoma (HSA) is most commonly identified in the region of the right atrium or right atrial appendage while chemodectoma (common in brachycephalic breeds) is most often identified at the heart base. Mesothelioma and any metastatic tumor are additional neoplastic causes. Although location and breed are frequently suggestive of tumor type, definitive diagnosis is dependent on a biopsy specimen.

Idiopathic pericardial effusion tends to be an inflammatory process and is frequently recognized in similar breeds to those that develop HSA. Significant efforts in recent years have been directed towards developing diagnostic tests to help differentiate malignant from benign pericardial effusion (idiopathic). Pericardial fluid pH was initially thought to aid in making this differentiation; however, pericardial fluid pH has now been clearly shown to be of little diagnostic value. Evidence suggests that blood concentrations of cardiac troponin I (cTnI) are significantly higher in dogs with masses consistent with HSA than in dogs without evidence of an underlying cause (idiopathic).

Vitamin K_1 antagonists (anticoagulant rodenticides and coumadin) can also result in pericardial effusion. Therefore, it is the author's practice to always perform an ACT or other point-of-care coagulation assessment prior to pericardiocentesis. If significant coagulopathy is present and patient condition permits, correction of coagulopathy with blood products (fresh frozen plasma or fresh whole blood) is indicated prior to pericardiocentesis. Subsequent institution of Vitamin K_1 therapy for 4 weeks is indicated.

Left atrial tear is an uncommon consequence of chronic mitral regurgitation and left atrial dilatation; however, it has been recognized as a cause of acute pericardial effusion in the dog.

An infectious cause of pericardial effusion is fungal disease (coccidiomycosis). Bacterial pericarditis and pericardial effusion secondary to trauma also occur, but are uncommon.

Numerous additional conditions such as congestive heart failure, uremia, decreased oncotic pressure, and a host of systemic inflammatory processes frequently result in small volume pericardial effusion accumulations without evidence of cardiac tamponade.

PERICARDIOCENTESIS

Pericardiocentesis can be a stressful procedure. Use of cardiovascularly sparing sedatives (opioids and benzodiazepines) may alleviate patient stress and facilitate safe pericardiocentesis. Numerous techniques have been described for pericardiocentesis in the dog including, but not limited to the use of a large-gauge over-the-needle catheter, through-the-needle catheter, and catheters placed using the Seldinger technique. The author prefers to use a 14- to 16-gauge, 5.5-inch over-the-needle catheter with two additional small side-holes or a commercial 6F multi fenestrated locking loop pigtail catheter (Infiniti Medical, New York, NY) placed using the Seldinger technique. The latter may be left in place for ongoing drainage.

The ECG should be monitored during and after pericardiocentesis for the presence of arrhythmias induced by catheter-associated irritation of the epicardium and decreased myocardial oxygen delivery experienced during cardiac tamponade. Lidocaine should be readily available, as should a defibrillator.

Pericardiocentesis is most often performed from the right hemithorax because injury to the left coronary artery is unlikely, and the cardiac notch is slightly larger. The patient can be positioned in sternal recumbency (preferred by most) or laterally. Full surgical preparation should be performed between the 2nd to the 8th ribs and from the mid-thorax to the level of the sternum. A fenestrated drape should be placed. Aseptic technique should be practiced at all times. The apex beat of the heart should be palpated (most often between the 4th and 5th ribs just above the costochondral junction) and lidocaine should be infiltrated locally off the cranial edge of the rib (to avoid the intercostal neurovascular bundle). Ultrasound guidance can also be used to identify the optimal location for pericardiocentesis. A small skin incision (<5 mm) should be made in the proposed insertion site and the catheter advanced through this incision (off the cranial edge of the rib). Upon the appearance of fluid in the flash chamber, the catheter and stylet should advance together for 2 to 3 mm and the catheter fed over the stylet into the pericardium. Initially, a small fluid sample should be placed in an ACT or clot tube. A sample retrieved from the ventricle should clot (unless the underlying condition is anticoagulant rodenticide intoxication) while one that has been in the pericardial space for any appreciable period of time should not. A fluid sample should be saved for cytologic analysis and culture and the pericardium should be evacuated.

MONITORING

Patient response to decompression of significant pericardial effusion is often very rapid and very gratifying as vital signs and physical examination findings improve dramatically. Monitoring for recurrence of fluid accumulation by frequent reassessment of major body systems, physical examination and echocardiography is useful.

PROGNOSIS

Prognosis for dogs with pericardial effusion will depend on the underlying cause of the disease. Surgical removal of a mass on the right atrial appendage will alleviate signs of acutely recurrent pericardial effusion. Surgical removal of right atrium/appendage hemangiosarcoma followed by chemotherapy will prolong life in dogs with pericardial effusion.[9] Pericardectomy will temporarily palliate clinical signs of pericardial effusion for most neoplastic processes, and will most often be curative for idiopathic pericardial effusion. Thoracoscopic pericardectomy or creation of a pericardial window may have similar effects.[10-11] Balloon pericardiotomy is currently under investigation as an alternative palliative procedure. Treatment with fresh frozen plasma, vitamin K1, and pericardiocentesis will be curative for dogs with anticoagulant rodenticide intoxication. Culture and sensitivity based antimicrobial therapy +/- surgical debridement is indicated for the management of infectious pericarditis. Dogs with left atrial tear secondary to chronic mitral valve regurgitation and left atrial dilation carry a guarded prognosis. Surgical repair of such a lesion has been described.[13]

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HYPERTENSION – TARGET ORGAN DAMAGE AND THERAPY

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WHAT IS HYPERTENSION?

Hypertension is a sustained elevation of blood pressure that is higher than "normal" for that patient. As routine measurements are not done in all clinics, we cannot always refer to the individual's normal blood pressure but have to compare it to either breed-specific values or according to normal ranges established by the Veterinary Blood Pressure Society and ACVIM Hypertension Consensus Group. Rather than speak of mild, moderate, or severe hypertension it is better to refer to the risk of end organ/target organ damage (TOD). Hypertension is not only a symptom of a disease but also a disease in itself as it causes damage, mainly to the eyes, the heart, the kidney and the brain.

Risk Categories	Systolic Pressure	Diastolic Pressure
I	<150	<95
II	150–159	95-99
III	160–179	100-119
IV	≥180	≥120

It is important to judge systolic and diastolic pressure individually as we can differentiate between:

- Isolated systolic hypertension: only systolic blood pressure is high, diastolic is normal
- Isolated diastolic hypertension: only diastolic blood pressure is high, systolic is normal
- Mixed hypertension: both systolic and diastolic blood pressure are elevated

Each type of hypertension occurs in dogs and cats and each type can cause TOD.

WHAT TYPE OF HYPERTENSION CAN BE FOUND IN DOGS AND CATS?

Dogs and cats, unlike human beings, suffer predominantly from secondary hypertension. That means that there is an underlying disease causing blood pressure to rise. In some individuals it is not yet possible to diagnose an underlying problem; these cases are referred to as "idiopathic hypertension." The ACVIM Hypertension Group recently published a consensus statement on blood pressure that establishes this terminology (J Vet Intern Med. 2007;21(3):542-558).

HOW DOES HYPERTENSION DEVELOP?

In most instances, hypertension develops because of increased vascular constriction, in some diseases such as hyperthyroidism increased cardiac output may also be a contributing factor. One of the main regulating systems responsible for hypertension via vasoconstriction is the renin-angiotensin-aldosterone system (RAAS), which is also activated in heart and renal insufficiency. Increased adrenergic tone or responsiveness to catecholamines may play a role in some diseases as well. In rare instances, blood viscosity can increase leading to hypertension. This can be the case with gammopathies (ehrlichiosis, multiple myeloma) or polycythemia. Depending on the underlying disease additional mechanisms can contribute to hypertension.

TARGET ORGAN DAMAGE AND THERAPY

The Heart as a Target Organ

High blood pressure means elevated preload but more importantly elevated afterload for the heart. Consequently the heart has to react to pressure load and compensate for the additional work. The increased wall tension is sensed by mechanoreceptors which then initiate the processes by which a variety of signals such as release of growth factors, intermediate peptides (eg, endothelin and angiotensin II) and alpha-adrenergic stimulation leads to changes in the myocardium. Both myocardial hypertrophy and myocardial hyperplasia occur. The result of both is more or less marked wall thickening (concentric left ventricular hypertrophy) and increase in heart muscle mass. By increasing wall thickness, wall stress is reduced (relationship of LaPlace); however, left ventricular compliance is reduced (decreased diastolic function). This hypertrophied cardiac muscle is more sensitive to adrenergic stimulation and ischemic injury. Growth factors together with tissue hypoxia stimulate collagen synthesis. Reduced diastolic function can result secondary to the chronic cardiac changes. RAAS activation may further induce increased arteriolar tone and increased coronary vascular resistance, in cats hypertrophy of the coronary arterioles has been reported (Littmann MP: Spontaneous systemic hypertension in 24 cats. J Vet Intern Med. 1994; 8(2):79-86)

Clinical Findings:

- **Auscultation:** Abnormal auscultatory findings are frequent in dogs and cats (70% of feline hypertensive patients in: Elliot et al, J Small Anim Pract. 2001;42;122-129). Cardiac murmurs are not infrequently encountered. This may also be partially caused by concurrent issues such as anemia from chronic renal failure or hyperthyroidism. Gallop rhythms are common because of decreased ventricular compliance. Arrhythmias can also occur, though they are more common when other diseases are present that predispose to them such as hyperthyroidism.
- **ECG:** Findings are not specific for hypertension. Common findings are tall R waves (high voltage), increased heart rate and less frequently taller P-waves and dysrhythmias.
- **Thoracic Radiographs:** Mainly left sided cardiomegaly, enlargement and tortuosity of the aorta
- **Echocardiography:** Left ventricular enlargement often with asymmetric or symmetric thickening of the

intraventricular septum and the left ventricular free wall. Mitral insufficiency is often detectable. Unlike with hypertrophic cardiomyopathy left ventricular diameters in diastole tend to be preserved.

The Kidney

In an animal with impaired kidney function, hypertension provokes a more rapid progression of the kidney disease, as it damages the nephrons and can contribute to proteinuria. This is especially true in patients with renal disease as they have lost autoregulation, in other words the ability of the kidney to control renal blood flow and GFR. This sets up a vicious cycle where kidney disease increases blood pressure which then increases loss of renal function. Renal failure undoubtedly is the leading cause of hypertension in small animal practice. With loss of autoregulation there is also a concomitant inability to maintain renal perfusion when hypotension occurs. This is especially important in patients with renal disease that are anesthetized. Hypertension (even with normal renal function) generally leads to a decreased ability to compensate for hypotension, renal failure can occur.

The Eyes

The eyes are commonly affected by hypertension and as a result retinal examination of all animals with suspected hypertension is recommended. Given that hypertension is most common in older patients including a retinal exam as part of the general physical exam in older cats should be considered. Blood supply to the retina is via the choroid and the retinal arteries. Retinal arteries have autoregulatory capability, as blood pressure increases they vasoconstrict. This is not true of the choroidal vessels. With prolonged hypertension this can lead to areas of ischemia with eventual rupture and hemorrhage (hypertensive retinopathy). With hypertensive choroidpathy, severe bullous retinal detachments are more common. A hypertensive optic neuropathy can also be encountered.

Clinical Findings. A variety of clinical signs can be seen. Hyphema can occur; often this results initially in uveitis;, with persistence, secondary glaucoma can result. Unilateral or bilateral mydriasis with poor to absent PLRs may be seen as may be blindness. Examination of the posterior segment will reveal retinal vascular tortuousity, hemorrhage and detachments. Older lesions may be present that reveal retinal degeneration and retinal hyperreflectivity. There are other diseases that can cause similar lesions such as vasculitis, hyperviscosity, bleeding disorders, etc.

The Brain

Although hypertension can cause damage to the brain it is important to remember that brain disease can lead to systemic hypertension as well via the Cushing reflex. If intracranial pressure increases there is a concomitant increased in systemic blood pressure to help maintain blood flow to the brain. The brain is another organ that possesses the ability to autoregulate blood pressure and blood flow to the brain. With hypertension, cerebral vessels are constricted to prevent the hypertension from being passed down to smaller arteries which would be more susceptible to injury and therefore potentially begin to hemorrhage. Persistent hypertension leads to chronic changes to blood vessels with hypertrophy. This can lead to areas of ischemia or hemorrhage. Hemorrhage into the brain is irritating resulting in inflammation (meningitis, myelitis, encephalitis). In the brain, hypertension can also result in edema which can further exacerbate dysfunction.

Clinical Findings. Clinical signs are relatively variable and can include behavior changes, depression, seizures, salivation, cranial nerve abnormalities, and potentially coma.

TREATMENT

Which Drugs Should be Considered?

- ACE Inhibitors, to:
  - Lower blood pressure (in general 10 to 20 mmHg) by reducing pre- and afterload
  - Will also have an anti-proteinuric effect that may be advantageous in some cases with renal disease
  - Will preferentially dilate the postglomerular (efferent) capillary, resulting in a decrease in intraglomerular pressure as well as GFR (usually only mild decrease in GFR resulting in mild increases in azotemia) even if the drop in blood pressure is modest. Though renal values may rise, this treatment will slow progression of renal disease by acting renoprotective.
- Dihydropyridin Calcium Channel Blockers (eg, amlodipine), to:
  - More aggressively lower blood pressure
  - Good efficacy and safety has been documented in cats
  - Preferentially dilate the preglomerular (afferent) capillary. This will maintain GFR, however if blood pressure reduction is not adequate, intraglomerular pressure can rise resulting in further loss of renal function.
- ß-blockers to:
  - Contribute to regression of left ventricular hypertrophy
  - Reduce heart rate
  - Especially if hyperthyroidism is concurrently diagnosed with cardiac changes
  - Efficacy unproven in veterinary medicine
- Diuretics, to
  - Further support diuresis, thus lowering pre- and afterload
  - Primary choice in humans, efficacy doubtful in small animal patients.

In summary, treatment should depend on the underlying disease, but adequate decrease of hypertension must be obtained.

SUGGESTED READING

1. Egner B, Carr A, Brown B (eds.): Essential Facts of Blood Pressure in Dogs and Cats. A Reference Guide. 2nd English ed. BE VetVerlag, 2007.

BLOOD PRESSURE MEASUREMENT: COMPARISON OF TECHNIQUES

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Blood pressure measurement becomes more and more of a routine procedure in veterinary practice. Although it is not a difficult task per se, there are some requirements which need to be followed to allow fast and reliable readings. However the most important prerequisite is **the willingness to measure blood pressure!**

Many authors described the influence of environmental stress but also the influence of an impatient examiner on blood pressure. Thus certain requirements have to be fullfilled to allow a relaxed and fast reading and reliable results:

- Blood pressure measurements should be taken in a quiet room
- Visitors or employees should not walk in and out of the room while a patient is measured
- The animal should have a few minutes to get used to the environment and the overall situation
- The animal should be handled in a calm and patient manner
- The pet's owner should be present provided he or she is able to calm the animal
- In each clinic, one or more individuals should be responsible for appointed to obtain blood pressure measurements to ensure consistent technique
- Measurements should be taken in a relaxed position
- The appropriate equipment should be used and limitations (Doppler, conventional oscillometry, plethysmography) should be well known to allow a correct interpretation of the results
- When using HDO technology, measurement is easiest on the base of the tail, but can also be obtained on the limbs

Allow the animal to adjust to the environment:

- Cats: Take the cat out of its kennel. Let the cat decide on the preferred position and whether to sit on the examination table or being held in the arm of the pet owner.
- Small dogs: The patient can be placed on the examination table or held by the owner
- Large dogs: If possible, take the measurements with the patient positioned on the floor

Positioning of the patient:

- It is most important that the measurement site is at about the level of the base of the heart.
- That can be ensured when measuring the patient in
    - "Down" position at the base of the tail or on the front limb below the elbow
    - Lateral recumbancy, with the cuff being placed on the base of the tail or that front limb, which is on the ground
    - Standing position, measuring on the base of the tail

BLOOD PRESSURE MEASUREMENT TECHNOLOGY

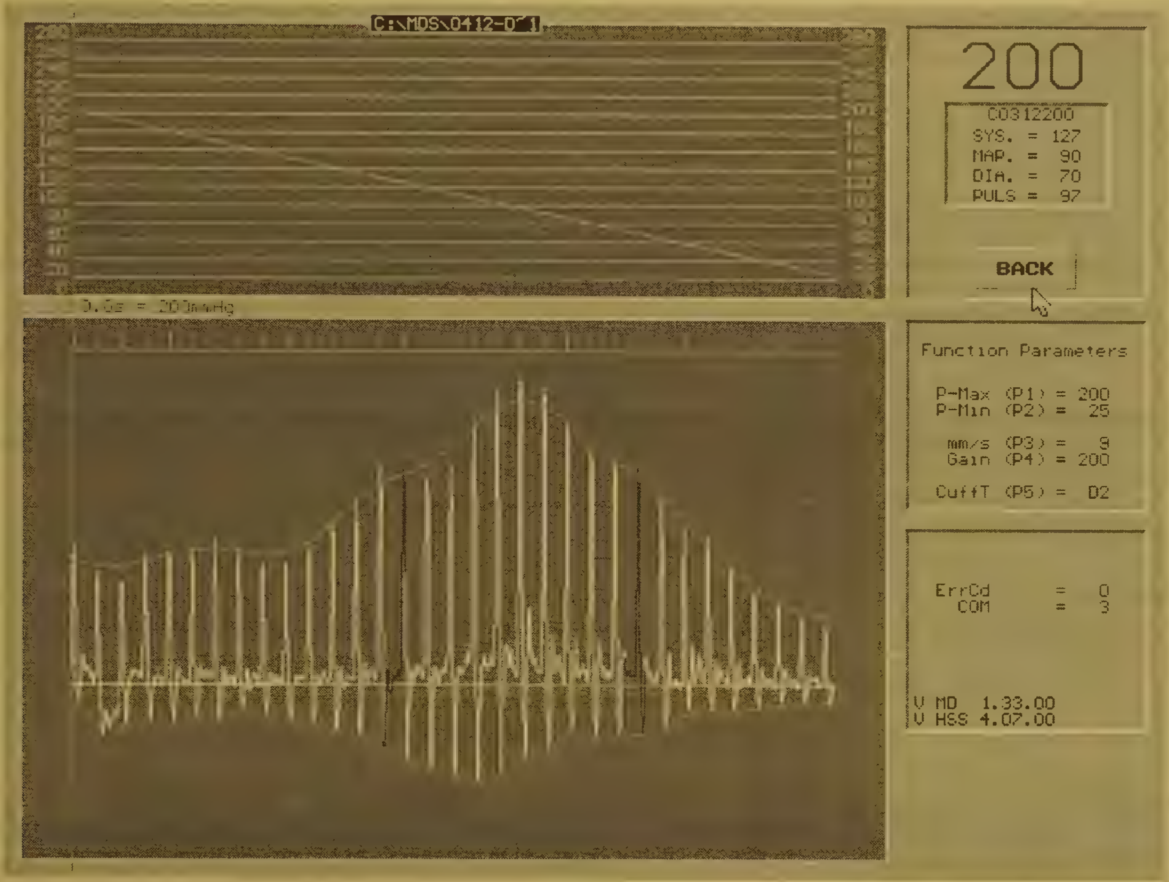
In general, since both the systolic and diastolic blood pressure are important to analyze, technology should be used that can measure both values.

Currently the most reliable of these technologies is HDO® (High Defintion Oscillometry), which just recently has been patented. It is a totally new technology with an algorithm developed specifically for animals. Due to its high-speed processor (32-bit compared with 8-bit of conventional oscillometric and invasive/direct units), it is the first technology allowing visible real-time measurements. Furthermore, HDO additionally offers GAIN, which magnifies very small amplitudes allowing measurements in a patient with shock or with arrhythmias. Another new feature of this technology is the individual adaption of deflation rate according to the pulse rate, allowing rapid blood pressure determination in animals with high heart rates, for example, cats.

With HDO a graphical display of the oscillations recorded by the blood pressure device is possible. Analysis of the graphs provides additional information regarding cardiac output and vascular status.

HOW TO INTERPRET THE GRAPHS?

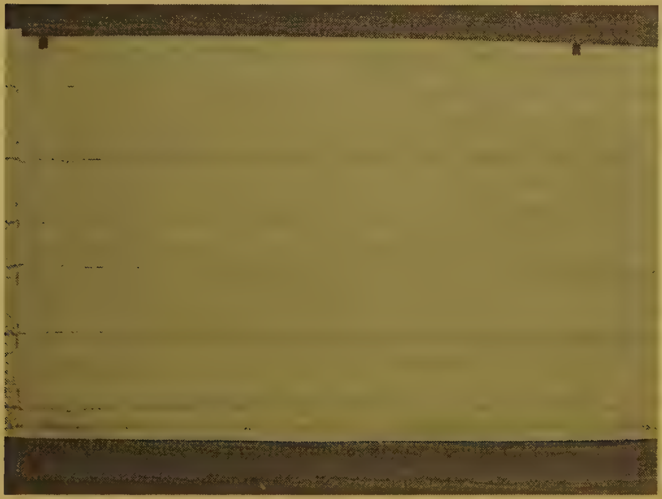
An HDO screen shot of a normal and regular rhythm, with constant cardiac output, is shown in Figure 1. Technical features of the different blood pressure measurement systems—Doppler, conventional oscillometry, and HDO—are listed in Table 1. Implications of the different technologies for practical applications are summarized in Table 2.



```
200
C0312200
SYS. = 127
MAP. =  90
DIA. =  70
PULS =  97

0.6s = 200mmHg

Function Parameters

P-Max (P1) = 200
P-Min (P2) =  25

 mm/s (P3) =   9
 Gain (P4) = 200

CuffT (P5) =  D2

ErrCd     =   0
  COM     =   3

V MD  1.33.00
V HSS 4.07.00
```

1220-132min

Figure 1. An HDO screen shot of a normal and regular rhythm, with constant cardiac output, is shown in Figure 1. Systolic and diastolic pressures are indicated as red- colored amplitudes. All parameters set can be viewed in the right window "Function Parameters."



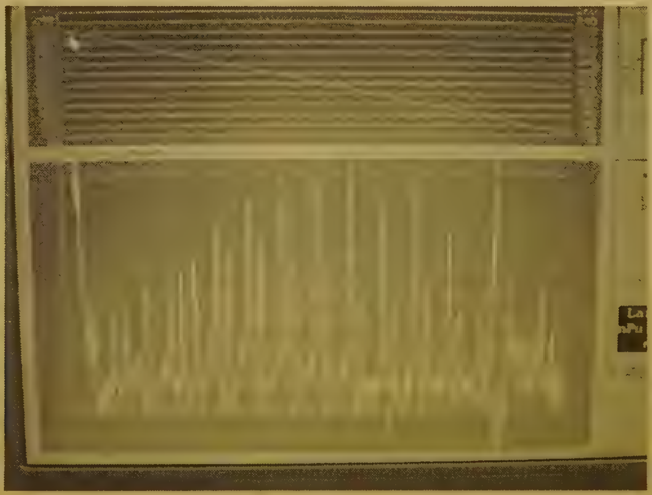


Figure 2. This in contrast is a patient with sinus block as it can be seen on the corresponding ECG. Different amplitudes indicate different cardiac output situation (prolonged diastolic filling during the block, thus higher CO after the block), block can also be seen on HDO as pauses.

Figure 3. The picture of, for example, premature beats can be very similar, so an ECG is still needed to characterize the arrhythmia found on the HDO-screen.

Table 1. Technical Features of the Different Blood Pressure Measurement Systems*

	Doppler	**Conventional Oscillometry**	**High-definition Oscillometry (HDO)**
Gain	Acoustic detection of the return of blood flow (dependent on the examiner's individual hearing capacity and reaction speed at which the examiner can visually observe and mentally register the numbers on the sphygmomanometer gauge)	Fixed preset values for recognition of pulse waveforms and amplitudes	Allows automatic or manual adjustment of amplitude recognition settings (amplification) for each individual patient (range: 70 to 640 X)
Artifact recognition	Not possible	Two approximation strategies are used (depending on manufacturer) • Fuzzy logic • Feedback loop	Recognized artifacts are eliminated and do not interfere with measurements
Valve action	Mechanical valve; Linearity from ~160–80 mmHg	Mainly mechanical valves; sometimes electronic valve Linearity from ~160–80 mmHg	Electronic valve Can be programmed towards a linearity of 0-300 mmHg
Pulse-dependent linear deflation rate / cutoff value	Valve-determined cutoff value at approx. 160 mmHg; Since the mechanical valve is opened manually, linear deflation of cuff is not possible	Valve-determined cutoff value at approx. 160 mmHg; Valve is opened automatically (mechanical or electronic valves, the sensitivity of which can be adjusted more or less variably); Real-time analysis and, hence, real-time valve programming is not possible (8-bit processor);	Valve-determined cutoff value at approx. 160 mmHg; Real-time analysis and real-time valve programming is possible in the 0–300 mmHg pressure range (32-bit processor)
Processor speed and sampling rate	Real-time analysis not possible; Dependent on the examiner's hearing and reaction capacity; Detailed analysis not possible	Real-time analysis not possible; Permits pulse rate-dependent analysis (160–250 max., depending on the system), on average, of one entire amplitude in a maximum measurement range of 0–250 mmHg	Permits real-time analysis; Provides much higher resolution and permits analysis within micro-seconds; can therefore detect even the smallest signals and measure extremely high heart rates of 400 beats/min and higher

* From B Egner, A Carr, S Brown (eds): Essential Facts of Blood Pressure in Dogs and Cats. A Reference Guide. 2nd English Edition, BE VetVerlag, 2007; with permission.

Table 2. Implications of the Dfferent Tchnologies for Pactical Aplications*

	Doppler	Conventional Ocillometry	High-Definition Ocillometry (HDO)
Specified measurement range	0–300 mmHg	0–300 mmHg	0–300 mmHg
Theoretical precision	~ 80–160 mmHg (valve) and user-dependent	~ 80–160 mmHg (valve) < 250 mmHg (processor)	0–450 mmHg (valve and processor)
Actual precision	? max 160 mmHg (User-dependent)	~ 80–160 mmHg	5–300 mmHg
Use of patient-specific measurement variables	Not possible	Manufacturer-dependent, maximum inflation pressure	Automatic calibration or manual adjustment of maximum inflation and deflation pressures, deflation rate and gain are possible
Cuff volume recognition	NO	NO	YES
Time per measurement in cats	approx. 30 seconds to 2 minutes *	approx. 40 seconds to 2 min **	8–15 seconds ***
Measurement despite arrhythmia	Not possible	Limited (fuzzy logic) / Not possible	Possible
Sensitivity at low amplitudes °	Limited; There is no gain option since signal amplification is linked with noise amplification	Manufacturer-dependent limitations; Preset optimizer for cats (Memoprint)	Gain options: 50–1200 MD Science; 70–640 MDPro; 140–400 MD90; 200–640 MD15
Deflation rate °°	»Click« at 3 mmHg/min; otherwise not definable	Generally 3 mmHg/sec; Memoprint: 3–6 mmHg/sec	Individual and pulse-dependent adjustment from 3–18 mmHg/sec (MD Science up to 27)
High heart rate	Impedes measurement considerably	Manufacturer-dependent limitations occur at 160 bpm and higher	≤ 400 beats per minute (bpm) with MD15, MD90, MD Pro; > 400 bpm possible with MD Science
Provision of measurement results	Acoustic signal, cuff pressure read from sphygmomanometer dial	Digital display of SAP, DAP, MAP (depending on manufacturer), and pulse	Real-time display of results on screen of laptop or PC (Fig. 1) or digital display for users without PC connection; graphics display can be analyzed on PC at a later time
Telemedicine capabilities [1]	NO	NO	YES
Measurements during anesthesia	May be limited (depending on which anesthetic is used)	May be limited (depending on which anesthetic is used)	No limitations apply
Measurement at very low pressures (SAP < 60 mmHg)	Not possible	Not possible	Possible
Automated monitoring function	NO	Feedback loop function on some systems (manufacturer-dependent)	Feedback loop function, real-time measurement recording and on-screen presentation

* From B Egner, A Carr, S Brown (eds); Essential Facts of Blood Pressure in Dogs and Cats. A Reference Guide. 2nd English Edition, BE VetVerlag, 2007; with permission.

SILDENAFIL – WHAT YOU NEED TO KNOW

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Pulmonary hypertension (PHT) is a life-threatening disease that is uncommonly diagnosed in canine patients. It is defined as an increase in pulmonary arterial pressures greater than 25 mmHg in systole and 15 mmHg in diastole. PHT is typically diagnosed in patients noninvasively via transthoracic echocardiographic estimations of pulmonary arterial pressure. There are numerous published etiologies for PHT traditionally divided into (1) primary or idiopathic PHT and (2) PHT secondary to an underlying disorder. Diseases that are commonly seen to result in secondary PHT include chronic respiratory disease (chronic bronchitis, interstitial lung disease, high altitude exposure), pulmonary thromboembolism, diseases causing increased left atrial or left ventricular end diastolic pressures (degenerative mitral valve disease, cardiomyopathies, congenital heart disease) or diseases directly affecting the pulmonary vasculature (heartworm disease). Most dogs with mild to moderate PHT are asymptomatic and thus are likely undiagnosed. Dogs with more severe PHT may present for exercise intolerance, syncope, lethargy or potentially signs of right-sided congestive heart failure. Treatment goals in patients with PHT include attempts to identify and treat any underlying etiology as well as management of signs of right-sided congestive heart failure should they exist. Effective management of primary/idiopathic PHT has historically been limited as most vasodilators exert a fourfold higher effect on the systemic vasculature than on the pulmonary circulation thus causing systemic hypotension long before any appreciable decrease in pulmonary pressures occur.

In the pulmonary vasculature, cyclic GMP (cGMP) allows for pulmonary vasodilation. Phosphodiesterase-5 (PDE-5) is an enzyme located primarily in the bronchi and trachea which is responsible for the breakdown of cGMP. An agent that selectively blocks PDE-5 should therefore increase cGMP levels in the pulmonary vasculature and cause pulmonary vasodilation with little effect on the systemic vasculature. Sildenafil (Viagra®) is a PDE-5 which has been used in humans and is now being used in veterinary patients for the treatment of primary PHT. Numerous, small, single-center case reports and case series have been published on the use of sildenafil in humans, and now in veterinary patients as well. Results from these studies indicate that there is improvement in clinical status, both in the short and long term, in patients treated with sildenafil for PHT caused by many etiologies.

Sildenafil is expensive, but certainly more tenable for veterinary medicine than other agents (such as prostacyclin analogues and endothelin receptor antagonists) routinely used in the management of PHT in humans. Sildenafil is currently the most extensively researched of the PDE-5 inhibitors, and has been shown to improve both exercise tolerance and quality of life in humans with PHT resulting in its FDA approval for the treatment of PHT.

Sildenafil is available in multiple tablet sizes but the cost per tablet is the same regardless of drug concentration (Pfizer, $9.90 per tablet regardless of size. Available tablet sizes include 100 mg, 50 mg, and 25 mg). Multiple dosages ranging from 20 mg to 80 mg three times a day have been used in humans with PHT. No increase in the efficacy was seen at the higher dosages and the currently recommended dose in humans is 50 mg every 8 hours. In order to minimize costs, at the author's institution, we purchase the 100 mg tablet and either quarter or halve this tablet, or have it reformulated to fit our patient's needs.

Stability of a reconstituted sildenafil liquid formulation has been reported. We typically start a patient at 1–2 mg/kg twice a day and try to up-titrate to a dosage of 2–3 mg/kg three times daily (over several weeks). In response to the effectiveness of treating PHT with Viagra®, Pfizer has now re-released sildenafil as Revatio® (Pfizer, $9.70 per 20 mg tablet). This formulation is quite expensive and is not used by the author. In conclusion, sildenafil has markedly improved our ability to reduce clinical signs and improve quality of life in patients with PHT. Sildenafil is routinely used at the author's institution in combination with other cardiac medications for the management of PHT and heart failure including pimobendan, digoxin, low-molecular-weight heparins, aspirin, ACE inhibitors, and furosemide.

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PIMOBENDAN AND HEART DISEASE – BREAKING UPDATE

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The majority of positive inotropic agents used today in the United States increase contractility by increasing cytosolic calcium. Increased intracellular calcium not only increases myocardial oxygen consumption, but can also lead to the development of dangerous arrhythmias. Phosphodiesterase III inhibitors, such as milrinone, were initially available as oral medications for chronic inotropic support, but were withdrawn from the market because of observed increased risk of sudden death in patients treated long term. Phosphodiesterase III inhibitors are still available and approved for intravenous acute inotropic support but the package insert gives a prominent warning regarding safety when given for longer than 48 hours.

Calcium sensitizing drugs were developed to function differently than conventional inotropic agents such as digoxin, milrinone, or dobutamine. Rather than causing an increase in cellular calcium, these agents were to sensitize the contractile apparatus to the existing level of calcium within the cell. Theoretically, these agents should increase contractile force without causing increase in cellular calcium and thus alleviate the concern of calcium-induced arrhythmias with use. This expectation has not been met in the case of several members of this group, including levosimendan and pimobendan, which also have phosphodiesterase inhibitory properties in addition to the calcium sensitizing properties.

Pimobendan (Vetmedin®) is a relatively new drug licensed for use in Canada and Europe for the treatment of congestive heart failure secondary to chronic mitral valvular insufficiency in dogs. Pimobendan is an orally active drug combining calcium sensitizing properties with cyclic AMP phosphodiesterase III inhibition. As such, it has both positive inotropic effects and peripheral vasodilatory effects, thus it is also called an "inodilator." The Food and Drug Administration has recently announced the approval of Vetmedin in the United States for the management of congestive heart failure in dogs due to chronic mitral valvular insufficiency or dilated cardiomyopathy. Chewable tablets were scheduled to be released and available for sale in September 2007.

Because of its phosphodiesterase activity, much concern has been raised regarding arrhythmogenesis with use of pimobendan. Drug trials in normal dogs treated with pimobendan did not find an increase in the incidence of arrhythmias. One veterinary clinical study evaluating use of pimobendan did find an increase in the number and severity of ventricular arrhythmias. This was a small study, in which half of the dogs enrolled were Doberman Pinschers with dilated cardiomyopathy (DCM), a disease frequently associated with malignant ventricular arrhythmias which progress naturally. This increase in arrhythmias may have just as likely been due to disease progression. Another clinical study in veterinary medicine found no increase in the frequency of ventricular arrhythmias following pimobendan therapy in dogs with degenerative mitral valve disease. Anecdotal evidence and clinical experience with pimobendan do not suggest any increase in dangerous arrhythmias with use; however, more studies and clinical experience with the drug are still needed to assess this aspect.

As an "inodilator," pimobendan incorporates properties that are very desirable in the clinical management of *systolic congestive heart failure* secondary to both DCM and chronic degenerative mitral valve disease (MVD) in dogs. Significant improvement in long-term survival and reduced severity of clinical signs has been shown in dogs with congestive heart failure due to DCM or MVD treated with pimobendan. Review of available data suggests that pimobendan appears to be safe and well tolerated when used in combination with conventional therapy (ACE inhibitors, digoxin, diuretics) in these patient groups.

While there appears to be ample evidence of the beneficial effects of pimobendan for patients with systolic congestive heart failure, there is not currently a consensus regarding use in patients with asymptomatic (pre-congestive) heart disease. Additionally, there is evidence that treatment with a positive inotropic agent such as pimobendan prior to the development of systolic myocardial failure can have deleterious effects. Experimental data have shown that valvular and parietal endocardial jet lesions could be induced within 4 weeks in healthy dogs even in the absence of previous valvular disease. In addition, clinical reports of dogs chronically treated with pimobendan have described adverse cardiac effects, such as increased regurgitant fraction and left atrial enlargement, which were in part reversed following cessation of pimobendan therapy. Moreover, a recent prospective study in dogs with naturally occurring mild, asymptomatic mitral valve disease treated with pimobendan demonstrated increased regurgitant fraction and induction of mitral valve lesions including acute focal hemorrhages, endothelial papillary hyperplasia, and infiltration of chordae tendinea with glycosaminoglycans. These reports raise an important issue: is pimobendan indicated in dogs without systolic myocardial dysfunction? While the answer is not entirely clear at this point in time, careful case selection when deciding when and how to use pimobendan is advised and at present, it should be reserved for use when systolic myocardial failure is detected or suspected.

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LOW-MOLECULAR-WEIGHT HEPARINS — HOW TO USE THEM

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Low-molecular-weight heparins (LMWHs) are an alternative to unfractionated heparin (UH) in the treatment of cats with, or with the potential for, thromboembolic disease. Although UH has been used for decades, our understanding of all of the pharmacological actions of this substance in animal patients is still incomplete. Recently, much work has been done on fractionating heparin into lower-molecular-weight forms since they appear to have advantages over UH in humans including a significant reduction in therapy-induced hemorrhagic complications and a more predictable anticoagulant effect without the need for traditional laboratory monitoring required by UH.

Important pharmacological differences exist between LMWH and UH. As a result, LMWH can selectively inhibit Factor-Xa to reduce the likelihood of thrombus formation, while minimally affecting clotting times. LMWHs play an important role in prophylaxis and therapy of humans with thromboembolic disease. LMWHs in human clinical trials have been proven safe and effective in preventing and treating venous, arterial, and intracardiac thromboembolism. Similarly, LMWHs have been discovered in both dogs and horses to be safe and well tolerated, with minimal side effects and no bleeding complications. LMWHs have also been shown in humans, dogs, and horses to have a minimal effect on the common coagulation tests (eg, thrombin time, activated partial thromboplastin time [APTT]) that are often used to monitor conventional heparin therapy.

In the cat, however, much less is known about LMWH administration. The proper dose, dosing interval, method of monitoring, side effects, and effectiveness of the different LMWH agents are still unspecified. Most current recommendations have been either speculated from studies in other species or are anecdotal from prior experience. This is unfortunate because aortic thromboembolism secondary to cardiomyopathy is a fairly common and serious disease of cats.

In attempts to identify a safe, easily administered, effective anticoagulant medication in cats, several small veterinary studies looking at LMWH in cats have been conducted. One pharmacokinetic study in 8 healthy cats suggested that therapeutic concentrations of anti-FXa (as defined in humans) were achieved with a 100 IU/kg once daily dose of dalteparin given subcutaneously. A dose of 200 IU/kg of dalteparin was also adequate, however, it caused a significant prolongation of the APTT. No clinical signs of bleeding or other problems related to drug administration were observed during this study. Another similar study using dalteparin in 8 normal cats at a dose of 100 IU/kg subcutaneously twice daily was used. The data from this study suggested that this dose of dalteparin was inadequate to achieve an anticoagulant effect. Other laboratory values, such as prothrombin time (PT), APTT, antithrombin III (AT III), platelet count, and packed cell volume, were not significantly affected by the LMWH. A third study evaluating enoxaparin (1 mg/kg) and dalteparin (100 IU/kg) at twice daily dosing suggested that while adequate effect (evaluated via anti-FXa values) was achieved 4 hours post LMWH administration, this effect was gone by 8 hours. Conclusions from this study were that cats receiving LMWH therapy needed more frequent dosing than twice a day in order to be effective. Lastly, an ongoing study being performed at our institution using enoxaparin (2 mg/kg) and dalteparin (200 mg/kg) administered twice daily had a variable effect on normal cats with some having profound elevations in anti-FXa levels and others having no increase above baseline. In cats with the highest levels of anti-Xa activity, elevated APTT values and increased bleeding and bruising following venipuncture were noted.

In conclusion, we have learned a lot regarding use of LMWH in cats but there is much we still do not know. We know that in normal cats, there appears to be tremendous variation in individual response to dosage. Dosages of 1 mg/kg enoxaparin and 100 IU/kg dalteparin, every 12 hours, subcutaneously, appears to be safe, and will be effective in achieving the human target anti-FXa activity levels in the majority, but not all, of cats treated. However, we do not know what anti-FXa activity level conveys protection from thrombosis and thromboembolism in normal cats, and know even less about this in cats with cardiomyopathy. Ideally, anti-FXa activity should be measured after 48 hours of use, to ensure any particular cat is not resistant to the drug. Increases in dosage (above 1 mg/kg enoxaparin and 100 IU/kg dalteparin, q 12 hours) should be initiated only when monitoring of anti-FXa levels is performed. The cost and availability of such testing, in addition to the expense of LMWHs, may potentially make this approach in veterinary medicine impractical.

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TREATING FELINE HEART FAILURE

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Cardioimyopathy—disease of the heart muscle—is responsible for more than 95% of feline heart disease. The most common cause of symptomatic heart disease is diastolic heart. Many affected cats remain asymptomatic for life, although the incidence is uncertain.

DIASTOLIC DYSFUNCTION

Diastolic dysfunction results from a wide range of heart muscle disorders that promote ventricular stiffness and loss of compliance via diverse mechanisms that alter loading conditions; increase myocardial mass (hypertrophy); cause myocardial injury (inflammation, myocytolysis, necrosis), repair (fibrosis, matrix changes), myocyte disorganization, or ischemia. Arrhythmias, heart failure, or thrombovascular complications can develop.

WHAT IS DIASTOLIC HEART FAILURE?

These changes can lead to increases in left ventricular filling pressure and mean left atrial pressure. The term *diastolic heart failure* refers to the development of pulmonary edema in cases of abnormal diastolic function in the setting of relatively normal contractility (systolic performance).

GOAL FOR MANAGING FELINE HEART DISEASE

The primary goal for managing heart disease is to improve survival by reducing morbidity and mortality. Most treatment strategies await validation.

MANAGEMENT OF THE ASYMPTOMATIC CAT

Ideally, treatment should prevent disease progression, reduce risk factors, or decrease morbidity and mortality. Presently, there is little data to guide whether therapies should be implemented throughout the lifetime, or indicate when or which treatment should be initiated. Nevertheless, certain circumstances appear to increase risk of cardiovascular morbidity and therefore merit consideration for therapy.

POTENTIAL CARDIOVASCULAR RISK FACTORS

Substantial abnormalities involving myocardial structure or function appear to promote adverse outcome, thereby providing the raison d'être for pharmacologic intervention. The following may warrant therapy, although efficacy remains to be proven.

Myocardial Infarction

Myocardial infarction may be inferred by echocardiography. Rationale for angiotensin-converting enzyme inhibitor (ACEI) therapy is based upon the potential of these agents to favorably influence ventricular remodeling and reduce mortality in people and in experimental animals. The rationale for beta-adrenergic blockers similarly includes reduction of infarct size, myocardial oxygen utilization, and reduced mortality.

Tachyarrhythmia

Rapid tachyarrhythmias can reduce cardiac filling, promote ischemia, and cause hemodynamic instability. Sustained tachyarrhythmias are usually associated with myocardial disease with attendant cardiac remodeling (myocyte necrosis, fibrosis, inflammation, and interstitial matrix changes). It is prudent to consider antiarrhythmic therapy in selected cases, particularly when the ventricular rate is rapid.

Massive Left Ventricular Hypertrophy (Severe Hypertrophic Cardiomyopathy [HCM])

Cats with greatly increased left ventricular mass (maximal diastolic septal or left ventricular wall thickness > 8 mm) may be at increased risk for cardiovascular events.

Syncope

Recurrent syncope is a risk factor for sudden death in humans with HCM, and retrospective feline studies have related syncope and poor outcome. Syncope can be associated with tachyarrhythmias, dynamic left ventricular (LV) outflow obstruction, and ischemia. Symptoms can often be managed successfully with beta-blockers to reduce or abolish LV outflow tract obstruction.

Spontaneous Echo Contrast ("Smoke")

Spontaneous echo contrast is associated with blood stasis. This finding is considered to presage thrombosis, is associated with increased thromboembolic risk, and should therefore warrant antiplatelet drugs (aspirin) and perhaps more aggressive therapies.

"Malignant" Familial History of Sudden Death (High-Risk Genotype)

Pedigrees may be identified with a documented heritable pattern of HCM with severe morbidity and mortality (eg, Maine coon cats). Early intervention with calcium channel blockers or beta-adrenergic blockers may be contemplated based on experimental considerations, which hold that a pathway to the phenotypic expression of LV hypertrophy is influenced by triggers such as higher LV pressure and work load.

Myocardial Failure

In some HCM cats LV remodeling from infarction or other causes results in reduced contractility (eg, fractional shortening typically 22% to 29%) and/or increases LV end-systolic dimension (>12 mm). Therapies include oral taurine supplementation, ACE inhibitors to counteract neurohormonal activation and reduce remodeling, and judicious beta-blocker therapy if myocardial infarction is suspected, or if tachyarrhythmia is encountered.

Arrhythmic Right Ventricular Cardiomyopathy

Cats with advanced structural lesions (eg, severe right ventricle (RV) dilation, ventricular tachycardia) may be at risk for congestive heart failure (CHF). ACEI and potentially, antiarrhythmics (sotalol) should be considered in such cases.

MANAGING DIASTOLIC HEART FAILURE

Acute CHF (Pulmonary Edema)

Pulmonary edema is rapidly progressive and life threatening. Diuretics represent the cornerstone for acute emergency management. Furosemide administered intravenously causes peak diuresis within 20 to 30 minutes; inhibits renal sodium tubular reabsorption or its accompanying anions; promotes brisk diuresis; and reduces vascular volume decreasing LV filling pressures (ie, cardiac preload) and pulmonary congestion. Initial dosage is 1 to 2 mg/kg IV every 30 to 60 minutes until dyspnea associated with congestion is reduced. Then, dosage frequency is reduced, typically to every 8 to 12 hours. Alternatively, after one or more IV boluses, furosemide is administered via constant rate infusion (ie, based upon estimated dose for 24 hours). Resolution of pulmonary edema may be enhanced by application of transdermal 2% nitroglycerin ointment, ¼ to ½ inch every 6 hours. To reduce nitrate tolerance, alternate 12 hours with and 12 hours without nitroglycerine therapy. Supplemental oxygen (40% to 60% O_2-enriched inspired gas) may improve pulmonary gas exchange. Clinical improvement and resolution of congestion is indicated by reduced respiratory rate and work of breathing, resolved lung crackles, and radiographic clearing of alveolar infiltrates (usually by 24 to 36 hours). Dehydration, azotemia, and hypokalemia can result from over-diuresis.

Chronic Maintenance Therapies

Chronic therapy is individualized to maintain a congestion-free state; prevent arterial thromboembolism; halt, slow, or reverse myocardial dysfunction (theoretically); promote enhanced quality of life; and prolong survival. Treatable and contributory diseases should be identified and managed (eg, systemic hypertension, hyperthyroidism, and anemia). Therapy for each case must be individualized.

Ideally, treatment should be guided by clinical evidence that one or more drugs are safe and effective. The foundation of evidence-based medicine is randomized clinical trials designed to evaluate effects of specific therapies on morbidity and mortality. To help assess scientific data with an evidence-based perspective, one widely held technique qualifies clinical data according to four categories of evidence type (eg, Type A evidence results from large, prospective, randomized, controlled clinical trials designed to assess treatment and outcome; type D evidence is anecdotal or personal experience).

Chronic therapies consider administering one or more agents that include a diuretic, ACEI, beta-blocker, or calcium channel blocker. Furosemide is gradually decreased to the lowest effective dosage, typically, 6.25 to 12.5 mg every 12 to 24 hours). Some cats remain stable on 1 to 2 mg/kg PO given every other day while in others, diuretics may be used twice weekly or even discontinued. Preliminary data (Fox PR, for the Multicenter Feline Chronic Heart Failure Study Group. Prospective, double-blinded, multicenter evaluation of chronic therapies for feline diastolic heart failure: Interim analysis. J Vet Intern Med. 2003;17:398) from cats recovering from first onset of diastolic heart failure, and treated with either once daily administration of atenolol, dilacor, enalapril, or placebo (with background furosemide (6.25–12.5 mg/day), suggested that survival was shorter in the beta-blocker group. There was no statistical difference in survival between cats who received placebo versus diltiazem (Dilacor®). Cats in the enalapril group did as well or better than the placebo group.

Recurrent Heart Failure

Upward diuretic titration may be necessary with recurrent CHF. Diuretic resistance may occur as heart failure progresses, and cats with recurrent CHF are likely to benefit acutely from intravenous furosemide which has higher bioavailability. Addition of a second diuretic (eg, thiazide 5 to 10 mg daily, or spironolactone 12.5 to 25 mg daily) is reserved for cases of diuretic resistance. It is prudent to assess BUN, creatinine, electrolytes, and blood pressure in anorectic cats. Addition of other drugs is contingent on individual needs and underlying disease. Appropriate tests should be performed as needed to assess for systemic and metabolic disease (anemia, hyperthyroidism), cardiac structure and function (echocardiography), and other relevant conditions.

Thromboembolism

Antiplatlet aggregating therapy is considered when severe left atrial enlargement is present, when spontaneous echo contrast is evident in the LA or LV, or when cats have had previous thromboembolic episodes. Aspirin may be used, dosed at approximately 81 mg PO every three days, although lower doses have been suggested. Other agents are presently under investigation such as clopidogrel (Plavix®), 18.75 mg PO every 24 hours. Low-molecular-weight heparin drugs are added when cats have thromboembolic complications. Fragmin® (100 U/kg every 12–24 hours SQ) or enoxaparine (1mg/kg every 12 hours SQ) have been used relatively safely for chronic management, (optimal efficacy may require higher frequency of administration for Fragmin or higher doses, but every 6 to 8 hour administration rates may be impractical for long-term administration). Because hyperkalemia can follow re-perfusion injury, continuous ECG monitoring is valuable during the first 3 days following thrombosis. Periodic evaluation of BUN and electrolytes are useful.

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ACUTE & CHRONIC CANINE HEART FAILURE: THE ROLE OF PIMOBENDAN

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Pimobendan has been licensed for use in dogs with heart failure since 2000 in many countries around the world, including Europe, Great Britain, Australia, Canada, and Mexico. Pimobendan is produced and marketed by Boehringer Ingelheim under the trade name Vetmedin®. Pimobendan was recently approved in the US for the treatment of canine heart failure due to dilated cardiomyopathy (DCM) and chronic degenerative valve disease (CVD).

Pimobendan is a novel agent with properties that are desirable in the management of the **clinical stage** of both DCM and CVD in dogs. **Preclinical heart disease** is defined as the stage of disease when a patient has evidence of cardiovascular disease but **currently and previously has no clinical signs** that can be attributed to their underlying cardiovascular disease—eg, clinically normal dogs with heart murmurs characteristic of CVD and or evidence of radiographic or echocardiographic left atrial enlargement who historically and currently have no clinical signs of cardiovascular disease. **Clinical heart disease** is defined as the stage of cardiac disease when a patient **has or had clinical signs** attributable to their cardiovascular disease—eg, cough due to cardiogenic pulmonary edema and or left atrial enlargement causing left main stem bronchial compression either at the time of the current exam or previously. Thus dogs with clinical disease may not have current clinical signs of cardiac disease if they are stable on cardiac medication. With perhaps the exception of a dog that was in heart failure due to a patent ductus arteriosus that was subsequently repaired dogs cannot go backward from the clinical stage of heart disease they can only become stable and free of clinical signs with appropriate therapy. The development of clinical signs attributable to underlying heart disease identifies the development of heart failure (HF). Independent of underlying etiology and species HF is defined as the inability of the heart to deliver adequate quantities of blood to meet metabolic tissue demands with normal filling pressures. Heart failure can be clinically classified as backward or congestive HF and or forward HF. Backward HF refers to the build up of fluid (congestion) and patients with backward HF can be considered 'WET.' Backward HF can be subdivided into right, left or biventricular backward HF. Clinical presentations suggestive of left sided congestive HF are those commensurate with cardiogenic pulmonary edema. Clinical signs suggestive of right sided congestive HF are those commensurate with ascites +/- pleural effusion. Forward HF refers to poor peripheral perfusion and patients with forward HF can be considered 'COLD.' Clinical presentations suggestive of forward HF are those commensurate with poor peripheral perfusion such as weakness, exercise intolerance or collapse.

THERAPEUTIC APPROACH TO HEART FAILURE

Some therapies for HF are independent of underlying etiology (nonspecific) and some target the abnormalities associated with the underlying etiology. For example, any patient with dyspnea due to severe cardiogenic pulmonary edema will benefit from, rest, oxygen and furosemide but only patients with ventricular systolic dysfunction would be expected to benefit from a drug that enhances the strength of ventricular contraction, such as pimobendan. In addition, consideration must be given to potential side effects and drug–drug interactions as well as client (cost and ease of administration) and patient (suspension, tablet, chewable) preferences.

We predominantly manage patients with clinical signs of backward HF. Isolated forward HF is rare however, patients with clinical signs of backward HF are at risk for the development of forward HF and thus management of backward HF should include therapies targeting preservation of perfusion. In general HF therapies aim to relieve/reduce clinical signs of backward HF, improve or prevent clinical signs of forward HF and prolong survival. Some medications work in more than one category enhancing their potential utility. For example pimobendan reduces preload and afterload through balanced arteriovenous dilation, improves ventricular systolic function, may help palliate clinical signs attributed to pulmonary artery hypertension and has salutary effects on maladaptive cytokine profiles in HF. Table 1 offers a summary of cardiovascular medications used in the management of DCM and CVD broken down by clinical stage: Clinical Stage (HF) versus Preclinical. Stage

THERAPEUTIC APPROACH TO BACKWARD HEART FAILURE (WET)

Relieve signs of congestion:

1. Abdominocentesis (dog) and pleurocentesis (rarely dog) as required
2. Preload reduction:
   2A–Plasma volume reduction (eg, diuretics such as furosemide, hydrochlorothiazide, spironolactone (especially right HF))
   2B–Venodilation (eg, nitroglycerine, pimobendan)
3. Dietary sodium restriction
4. Inhibition of the rennin angiotensin aldosterone system (RAAS), (eg, angiotensin-converting enzyme inhibitors (ACEI) such as enalapril or benazepril and aldosterone antagonists such as spironolactone)

THERAPEUTIC APPROACH TO FORWARD HEART FAILURE (COLD)

Improve forward cardiac output:

1. Tolerable afterload reduction: Contraindicated in canine subaortic stenosis (eg, ACEI, hydralazine, amlodipine, pimobendan, Na nitroprusside (IV)).
2. Enhance systolic function in diseases characterized by systolic dysfunction such as canine DCM and

CVD (eg, pimobendan, dobutamine (IV), digoxin (weak inotrope)).

3. Treat clinically important (hemodynamically significant) arrhythmias:
   3A–Tachyarrhythmias; Ventricular (eg, lidocaine (IV), procainamide, sotalol, mexilitine, amiodarone), Supraventricular (eg, digoxin, beta-blocker, calcium channel blocker, amiodarone)
   3B–Bradyarrhythmias: Pacemaker, anticholinergics (eg, propantheline bromide), sympathomomemtics (eg, terbutaline), other (eg, theopylline)
4. Treat pulmonary artery hypertension if present and contributing to clinical signs: Phosphodiesterase V inhibition (eg, sildenifil, +/- pimobendan)

THERAPEUTIC APPROACH TO ALL PRECLINICAL AND CLINICAL HEART DISEASE

Agents in this category aim to prolong the preclinical stage in patients with preclinical heart disease and prolong survival in patients with HF.

Delay disease progression (prolong survival):

1. Inhibition of the RAAS:
   1A–ACEI (eg, enalapril, benazepril)
   1B–Aldosterone antagonism (eg, spironolactone)
2. Inhibition of the sympathetic nervous system:
   2A–Beta blockers (eg, atenolol & metoprolol (selective), propranolol (nonselective))
   2B–Adrenergic blockers (alpha & beta blockade), (eg, carvedilol)
3. Other: Modulation of cytokine maladaptation (eg, pimobendan)

PIMOBENDAN BACKGROUND

Pimobendan is a benzimidazole pyridazinone derivative and is classified as an inodilator (i.e., positive inotrope and balanced arteriovenous dilator). In failing hearts it exerts its positive inotropic effects primarily through sensitization of the cardiac contractile apparatus to intracellular calcium. As a phosphodiesterase (PDE) III inhibitor it can potentially increase intracellular calcium

Table 1. Summary of Cardiovascular Medications used in the Management of CVD and DCM

Disease		Preclinical Stage	Clinical Stage
CVD	Sinus rhythm	NT [2], ACEI [2], β-blocker [2]	Diuretic (furosemide) [4]*, Pimobendan [5]*, ACEI [5], spironolactone [4], β-blocker [1]
	Atrial fibrillation or other supraventricular arrhythmias (including sinus tachycardia)	NT [2], β-blocker [2], ACEI [3]	**As per sinus rhythm and add**: amiodarone [4], digoxin [3], β-blocker [3], CCB [2] *Note: combination therapy may be necessary*
	Ventricular arrhythmias	NT [2], β-blocker [3], ACEI [3]	**As per sinus rhythm and add**: sotalol [3], β-blocker & mexilitine [1]
	Left atrial enlargement causing left main stem bronchus compression	NT [2], ACEI [2], β-blocker [2]	**As per sinus rhythm and add**: theophylline SR [4], hydrocodone [3]
	Pulmonary artery hypertension	ACEI [2], β-blocker [2]	**As per sinus rhythm**: ↑ pimobendan dosing frequency to 3 times daily [5] and/or add sildenafil [4]
DCM	Sinus rhythm	ACEI [5]*, β-blocker [3]	Diuretic (furosemide) [4]*, Pimobendan [5]*, ACEI [5]*, spironolactone [4], β-blocker [1]
	Atrial fibrillation or other supraventricular arrhythmias (including sinus tachycardia)	β-blocker [3] + ACEI [4]	**As per sinus rhythm and add**: amiodarone [4], digoxin [3], β-blocker [3], CCB [2] *Note: combination therapy may be necessary*
	Ventricular arrhythmias	ACEI [4], β-blocker [3]	**As per sinus rhythm and add**: amiodarone [4], sotalol [3], β-blocker & mexilitine [1]

For definitions of Preclinical and Clinical disease stages see the preceding text. There is no definitive proof that any medication used during the preclinical stage of DCM or CVD can prolong the preclinical stage, thus the numbers in [ ] represent the authors current recommendations and no therapy (NT) is always an option.

Drugs are listed by class (eg, ACEI) and if there is a preferred drug within a class it will follow in brackets. Each class or specific drug listed is scored between 1 and 5 where [1] means rarely used for the indication and [5] means always used unless there is a clinical contraindication. Diuretic (furosemide) is always used if congestion is or was present.
* denotes which medication should be used if number of medications to be used is limited. This summary is based on professional opinion/experience and currently available peer reviewed data and can be expected to evolve over time.

Abbreviations: Angiotensin-converting enzyme inhibitor (ACEI), beta-blocker (β-blocker), calcium channel blocker (CCB), No therapy (NT).

concentration and increase myocardial oxygen consumption. However, the cardiac PDE effects of pimobendan are reportedly minimal at pharmacologic doses in dogs with heart disease, which is a major advantage relative to other inotropic PDE inhibitors such as milrinone. Pimobendan's calcium sensitization of the contractile apparatus is achieved by enhancement of the interaction between calcium and the troponin C complex resulting in a positive inotropic effect that does not increase myocardial oxygen consumption. Overall, pimobendan enhances systolic function by improving the efficiency of contraction, limiting the arrhythmogenic side effects of other positive inotropes whose sole mechanism of action is to increase myocardial intracellular calcium. Calcium sensitizers such as pimobendan may thus represent the only class of inotropic agents that "safely" augment contractility.

Phosphodiesterase III is found in vascular smooth muscle. Inhibitors of PDE III such as pimobendan result in balanced vasodilation leading to a reduction of both cardiac preload and afterload, a cornerstone of therapy in HF. PDE V concentrations may be higher in the vascular smooth muscle of pulmonary arteries, thus any nonselective PDE inhibition may help ameliorate elevations in pulmonary artery pressure (pulmonary artery hypertension) that tend to parallel long-standing elevations in left atrial pressure, a clinically important complication of CVD.

The significance of alterations in pro-inflammatory cytokine concentrations such as tumor necrosis factor-α, interleukins 1-β and 6 on the progression of HF has been documented in many etiologies of heart disease. Alterations in these cytokine concentrations are associated with increased morbidity and mortality. Pimobendan has demonstrated beneficial modulation of a several such cytokines in various models of HF, representing an additional potential benefit.

PIMOBENDAN THERAPEUTIC RATIONALE

Tolerable reductions in cardiac preload and afterload through balanced venous and arterial dilation are desirable in dogs with HF secondary to either CVD or DCM. The usefulness of "safe" augmentation of contractility is obvious in DCM (because it is characterized by global systolic dysfunction), but is not so obvious in CVD. Dogs with CVD develop compensatory left ventricular remodeling in the form of eccentric hypertrophy (dilation). Left ventricular (LV) systolic function is often thought to be preserved until relatively late in the course of CVD, based on normal or exuberant echocardiographic indices of LV ejection such as fractional shortening. However, interrogation of cardiac function by more sophisticated techniques has demonstrated reductions in LV systolic function in an experimental canine model of mitral regurgitation (MR) and in chronic primary MR of humans, a condition very similar to canine CVD.

Impaired systolic function in cases of HF secondary to CVD may contribute significantly to clinical signs of lethargy and exercise intolerance from reduced forward cardiac output. Although diuretics can relieve signs of congestion, they do little to alleviate and may exacerbate clinical signs of forward HF. Traditionally, dogs with HF secondary to CVD have been managed with judicious afterload reduction using agents such as ACEI alone or in combination with more potent arteriolar dilators (ie, hydralazine, amlodipine). Afterload reducing agents attempt to lessen the differential in pressure between the periphery and the left atrium thereby reducing regurgitant flow resulting in augmentation of forward cardiac output. However, dogs with advanced CVD often do not tolerate afterload reduction well. Frequently, clinical signs of forward HF do not resolve and may be exacerbated by overzealous afterload reduction, further impairing quality of life. Additionally, many dogs with advanced CVD and DCM have severe left atrial and ventricular dilation leading to mitral annular dilation, causing secondary functional MR. Other therapies for chronic valvular disease involve surgical mitral valve repair and mitral annuloplasty; however, these options are not routinely available for canine patients. Furthermore, many dogs with advanced HF due to CVD or other concurrent serious diseases such as chronic renal insufficiency are not good candidates for open-heart surgery even if clients wish to pursue this option.

If a potent positive inotropic agent such as pimobendan could enhance mitral annular and LV papillary tone, thereby optimizing the geometry of the LV and mitral apparatus, functional MR might be reduced leading to augmentation of forward cardiac output, thereby making any concurrent reductions in afterload better tolerated. This combined mechanism of action could be considered a pharmacologic annuloplasty. Reductions in regurgitant fraction may also result in beneficial reverse remodeling (ie, reduction in size) of the LV and left atrium. This constellation of hemodynamic effects may also indirectly modulate neurohormonal systems responsible for the progression of heart failure.

SUMMARY

Pimobendan is a novel agent with properties that are highly desirable in the clinical management of HF secondary to both DCM and CVD in dogs. Review of available data suggests that pimobendan is safe, well tolerated, and leads to enhanced quality of life in dogs with HF secondary to DCM or CVD when used in combination with furosemide or other conventional therapies (eg, ACEI, digoxin, spironolactone). Pimobendan leads to a reduction in mortality from HF associated with DCM and CVD and an ongoing study (QUEST) will offer additional insight into its effects on mortality associated with HF due to CVD.

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HEART FAILURE AND CHRONIC KIDNEY DISEASE: WHEN WORLDS COLLIDE

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Chronic valvular heart disease (CVHD) or endocardiosis is the most common acquired heart disease of dogs. Degeneration of the mitral valve characterized by myxomatous proliferation and fibrosis can result in valvular insufficiency and eventually congestive heart failure (CHF). Chronic kidney disease (CKD) is also a common problem that is irreversible and often progressive. Both CVHD and CKD are more prevalent in older dogs and when they occur together, patient management can be challenging. The decreased cardiac output that can occur with CVHD/CHF has the potential to further compromise renal function in CKD patients. Usually the adverse affect of CVHD/CHF is pre-renal in nature but in severe cases, poor renal perfusion can result in additional loss of nephrons, hastening the progression of the CKD. Increasing cardiac output is a major therapeutic goal in patients with CVHD/CHF and the resulting increase in renal perfusion will often also improve renal excretory function.

CHRONIC VALVULAR HEART DISEASE (CVHD)/CONGESTIVE HEART FAILURE

The left atrioventricular (AV; mitral) valve is most commonly affected with CVHD, although in about 30% of cases, the right AV (tricuspid) valve can also be also affected. The disease is approximately 1.5 times more common in males than in females, and it is much more common in small breed dogs. Commonly affected breeds include miniature poodles, chihuahuas, dachshunds, beagles, cocker spaniels, Maltese, Yorkshire terriers, and Shetland sheep dogs. Cavalier King Charles Spaniels (CKCS) are especially predisposed to developing heart failure at a young age from CVHD. The pathologic lesion involves changes in the glycosaminoglycan structure of the intercellular matrix of the valve apparatus (including the valve leaflets and chordae tendinea). These structural changes result in subendothelial thickening and rolling of the valve edges, with eventual deformation of the valve resulting in insufficiency and regurgitation. The prevalence of the pathologic finding increases markedly with age. The factors that cause and/or determine the progression of the lesion are not known; not all dogs with CVHD lesions develop CHF.

Clinical Recognition

The first clinical sign of the disease is the typical murmur of mitral regurgitation, which is usually, heard best at the left apex or midway between the apex and the base. The murmur is typically noted as an incidental finding during routine physical examination. The intensity of the murmur of mitral regurgitation does not always correlate with the hemodynamic significance of the murmur, although in all cases a murmur should be present. In CKCS, it has been demonstrated that the intensity of the murmur generally increases as the mitral regurgitation worsens, probably because the heart gets larger and is acoustically better coupled to the chest wall. This relationship between murmur intensity and severity may not be present in severe heart failure, where the murmur may actually become softer. The presence of a typical left apical regurgitant murmur in a coughing animal does not necessarily mean that the clinical signs present are secondary to CVHD and subsequent CHF, since both bronchial disease and CVHD may exist in the same patient. The patient signalment and history should be examined carefully to try and determine the cause of clinical signs in animals with CVHD murmurs. For example, overweight dogs with no history of weight loss and dogs with marked sinus arrhythmia and relatively slow heart rates are less likely to be coughing due to CHF. Clinical signs of CHF, if present, generally reflect left or biventricular failure and include dyspnea, cough, exercise intolerance, weight loss, and occasionally abdominal distention. Common causes of decompensation in dogs with CVHD include ingestion of a salt load (eg, potato chips), onset of a sustained supraventricular tachyarrhythmia (usually atrial fibrillation), rupture of a chordae tendinea with subsequent worsening of valvular regurgitation, or tearing of the left atrium and subsequent cardiac tamponade.

Modified New York Heart Association Classification (modified from Haggstrom, 2002)

- Class I – Normal activity does not produce undue fatigue, dyspnea or coughing
- Class II – Dog is comfortable at rest but (heavy) physical activity produces fatigue, dyspnea, or coughing; this classification might also include dogs with cardiomegaly but no signs early in this phase.
- Class III – Dog is comfortable at rest but minimal exercise produces signs. Also, orthopnea may exist in this phase.
- Class IV – Congestive heart failure, dyspnea, cough, fatigue, or ascites present at rest.

CHRONIC KIDNEY DISEASE

Nephron damage associated with CKD is usually irreversible and can be progressive. Renal failure results when three-quarters or more of the nephrons of both kidneys are not functioning. Whether the underlying CKD primarily affects glomeruli, tubules, interstitial tissue, or renal vasculature, irreversible damage to any portion of the nephron renders the entire nephron nonfunctional. Healing of irreversibly damaged nephrons occurs by replacement fibrosis and therefore a specific etiology is often not determined. Chronic kidney disease occurs over a period of weeks, months, or years and is an important cause of death in dogs. It is often not possible to improve renal function in CKD and therefore treatment is aimed at stabilizing renal function. Importantly, there is increasing evidence that dietary and antihypertensive treatments can decrease the progressive nature of CKD.

Etiology

The cause of canine CKD is often difficult to determine. Due to the interdependence of the vascular and tubular components of the nephron, the end point of irreversible glomerular or tubular damage is the same. Morphologic heterogeneity between nephrons exists in the chronically diseased kidney with changes ranging from severe atrophy to marked hypertrophy. The histologic changes are not process specific and, therefore, an etiologic diagnosis is frequently not possible. Renal diseases that have been associated with the development of CKD in dogs include glomerulonephritis, amyloidosis, tubulointerstitial disease, pyelonephritis, nephrolithiasis, leptospirosis and neoplasia. Progressive diseases that destroy nephrons at a slow rate allow intact nephrons to undergo compensatory hypertrophy, which can delay the onset of renal failure. Therefore, when renal failure finally occurs, nephron hypertrophy can no longer maintain adequate renal function and less than 25% of the original nephrons are functional.

Staging of Canine CKD

The International Renal Interest Society (IRIS) has proposed a staging system for CKD, which uses serum creatinine concentrations as the major determinate for the staging. As part of the initial diagnosis, serum creatinine concentrations should always be interpreted in light of the patient's urine specific gravity and examination findings in order to rule out pre- and post-renal causes of azotemia. This staging system should only be applied to dogs with stable CKD since in other forms of renal disease (eg, acute renal failure or acute decompensation of CKD); the plasma creatinine concentration can change significantly over a short period of time. In dogs with CKD, staging the disease helps the clinician specifically tailor diagnostic and therapeutic efforts to the individual patient. A guide to staging canine CKD was developed by the IRIS Board (Table 1).

The classic diagnosis of renal failure based on renal azotemia (persistent azotemia superimposed on the inability to concentrate urine) pertains to CKD in later stage II through IV. CKD that is categorized as stage I and early stage II CKD (non-azotemic CKD) could be diagnosed in dogs with persistent proteinuria, urine concentrating deficits, increases in serum creatinine over time that remain in the normal range (eg, serum creatinine that increases form 0.6 to 1.2 mg/dL could indicate a 50% reduction in GFR), or abnormal renal palpation or renal ultrasound findings. The above stages are further classified by the presence or absence of proteinuria and systemic hypertension as shown in Table 2.

Table 1. Guide to Staging Canine CKD Developed by the IRIS Board

Serum Creatinine Concentration	Stage I Non-azotemic CKD	Stage II Mild renal azotemia	Stage III Moderate renal azotemia	Stage IV Severe renal azotemia
mg/dL	<1.4	1.4–2.0	2.1–5.0	>5.0
µmol/L	<125	125–179	180–439	>440

Table 2. Classification of Renal Failure Base on the Presence or Absence of Proteinuria and Systemic Hypertension

Urine Protein/Creatinine Ratio	Classification
< 0.2	Non-Proteinuric
0.2–0.5	Borderline Proteinuric
> 0.5	Proteinuric

Systolic Blood Pressure (mm Hg)	Classification
< 140	Normotensive
140–160	Borderline Hypertensive
> 160	Hypertensive

MANAGING DOGS WITH BOTH CHF AND CKD

Prior to initiating treatment in dogs with CHF, it is important to evaluate renal function. For example, urine specific gravity will be of little diagnostic significance once Lasix treatment has been started. Furthermore, azotemia observed in dogs with CHF is often prerenal in origin and some degree of azotemia (≤30% increase over baseline values) is expected with aggressive management of CHF. When increasing azotemia associated with CHF treatment is of concern, decreasing the Lasix dosage should be the first option pursued.

Managing the patient with both CKD and CVD/CHF requires balancing the tendency to "dry-out" CHF-patients, while "hydrating" those with CKD. These two approaches are often at cross-purposes in the patients under discussion here. Reduction of signs of congestion with for example diuretics lowers cardiac output and thereby renal perfusion, increasing azotemia. In dogs with advanced stage CHF and advanced Stage CKD, strong inotropic support (eg, pimobendan) may be helpful in improving renal perfusion. Hypertension and proteinuria are commonly associated with CKD and complicate the management of these patients and reduce the prognosis. It is now well established that the presence of proteinuria is worsens the prognosis in CKD and is thought by many to contribute to the progression of CKD. Furthermore, systemic hypertension complicates cardiac disease by reducing forward cardiac output. In dogs with CVHD, the detection and correction of systemic hypertension is particularly important because hypertension increases mitral regurgitant flow, in addition to reducing cardiac output, and contributes to the worsening of endocardiosis left atrial enlargement. The latter increases the potential for the development of atrial fibrillation. Because of RAAS and sympathetic nervous system activation, ACEI treatment is foundational for the management of hypertensive and/or proteinuric CKD and CVHD/CHF.

Because anemia is problematic in CHF management in man, presumptively it contributes to the signs and negative prognosis of CHF in dogs. Anemia frequently complicates CKD and as such should be addressed here. There are no data on anemia in cardiac disease in animals to the authors' knowledge but for the motivated client, erythropoietin can improve the quality of life for many dogs with CKD. Because of the potential for binding antibody formation, erythropoietin treatment is usually reserved for those dogs with CKD with weakness and marked lethargy attributable to their anemia. Whether erythropoietin should be used earlier in dogs with both CKD and CVHD/CHF remains to be determined.

Although beyond the scope of this discussion, it is important for the clinician to be aware of the cardiac drugs which are renally excreted and which might require special observation or dosage alteration in cardiac patients with concurrent CKD. Examples of this include digoxin, the ACE-I, enalapril and the beta-blocker atenolol. Each will achieve higher serum levels, though not necessarily harmful, when GFR has fallen in CKD.

The authors' approach to managing and prognosticating various combinations of CKD and CVHD/CHF is outlined below. Key points include:

1. ACE-I remain the cornerstone in the management of CHF and proteinuric and/or hypertensive CKD.
2. Diuresis lowers cardiac output and renal perfusion; therefore will increase BUN and serum creatinine concentrations. If azotemia develops and must be treated, reduction in (or discontinuance) the diuretic dosage should be the first-line approach, with reductions in ACE-I only if necessary. The ACE-I should be reinstituted as soon as feasible, with diuretic use following only as needed.
3. Much of the azotemia observed in CHF-treated dogs is largely pre-renal and, as such, treatable. A certain degree of azotemia may be necessary in the treatment of CHF.
4. Treatment must balance the traditional "drying" efforts of CHF-management with the "hydrating" efforts used in CKD.
5. Rehydration should include relatively salt-poor fluids in dehydrated and azotemic patients with CVHD/CHF.
6. Hypertension worsens both CVHD/CHF and CKD. As such, it should be sought out, recognized and managed.
7. Pimobendan, in addition to being a new and important new drug in our treatment of CHF, may help us to improve renal perfusion, reducing azotemia in cardiac patients.
8. Proteinuria worsens the prognosis of CKD. It should be monitored and treated (ACE-I).
9. CKD may affect the excretion of cardiac and other drugs. The dosage of these drugs should be adjusted as necessary.
10. The prognosis for true renal failure (IRIS Phase 4 CKD) and severe CHF (NYHA Phase 4) is poor.

PATENT DUCTUS ARTERIOSUS: NEW TREATMENT OPTIONS

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Patent ductus arteriosus (PDA) is one of the most common congenital heart defects in dogs and is associated with profound hemodynamic alterations. It results from a failure of the left sixth aortic arch to close following birth allowing blood to shunt from the descending aorta into the pulmonary artery when body pressures are normal. The resultant left to right shunting leads to volume overload of the left heart and subsequent congestive heart failure if left untreated. Poodles, collies, Pomeranians, Shetland sheep dogs, Maltese, English springer spaniels, keeshonds, and Yorkshire terriers are all considered to be predisposed to having PDA. German shepherds and New Foundland dogs are two large breeds that also commonly present with PDAs.

DIAGNOSIS

The diagnosis of PDA usually can easily be made based on physical examinations findings. Auscultation of a continuous heart murmur over the left cranial thorax in the left axillary region and the femoral pulses are hyperkinetic. A secondary systolic murmur over the left 4th to 6th intercostal space may also be ausculted and is often due to mitral regurgitation the is the result of mitral annular dilation. Other physical examination findings might include signs consistent with left sided congestive heart failure including increased lung sounds, crackles and wheezes. Beyond physical examination other diagnostics such as electrocardiogram, radiographs, and echocardiogram are used to confirm suspicion based on the physical exam and to rule out other congenital heart defects that might complicate the treatment. Some common abnormal findings based on these diagnostics are listed below.

- **Electrocardiography**
  - Sinus tachycardia, atrial premature complexes, or atrial fibrillation
  - +/- Signs of left ventricular (LV) and/or left atrial (LA) enlargement
- **Thoracic radiography**
  - Left ventricular, +/- atrial enlargement
  - Pulmonary overcirculation – enlarged pulmonary arteries and veins
  - The classic "Ductus bump"
  - Dilation of the main pulmonary artery (PA)
  - Pulmonary venous congestion and pulmonary edema
- **Echocardiography**
  - LV, +/- LA dilation
  - MPA dilatation
  - Visualize the ductus
  - Reduced percent fractional shortening (%FS)
  - Continuous retrograde flow in the PA, +/- mitral regurgitation (MR), +/- pulmonary insufficiency (PI)
  - Exaggerated aortic flows

We also utilized echocardiography to get a preliminary idea of the size of the ductus so that we can plan the appropriate treatment options.

Definitive therapy for PDA involves closure of the ductus. Traditionally in veterinary medicine, surgical ligation of the ductus via lateral thoracotomy is highly successful for correction of this defect. However, surgical options have been associated with increased morbidity, and arguably increased hospital stays and cost compared with newer transcatheter techniques. Since its first reported use in dogs in the late 1990s; transcatheter measurements have become a popular and successful alternative to surgery among veterinary cardiologist, paralleling the trend in human medicine. It is important to remember with new techniques comes new growing pains in the search for the ideal device to "replace" the surgical gold standard. Ideally this device would satisfy most of the following criteria: It could be delivered via a small catheter to suit our small patients, delivery could be controlled to allow repositioning of the device and could be retrievable, it would provide complete occlusion with no obstruction to normal flow, it could be used in the different morphologic forms of PDA, and it would be comparable to if not better than surgery as it pertains to complications and cost. A number of techniques and devices have been developed and used over the years; however, three devices have proven to be the most amendable for therapy for canine PDA: vascular occlusion coils, the Amplatz vascular plug, and the Amplatz canine vascular occlusion device.

While transcatheter closure of the PDAs requires specialized equipment and training and is not performed in general private practice, it is imperative for the private practitioner to have a basic understanding of treatment options, their outcomes and complications to provide the most essential information to their clientele regarding treatment options for this disease.

ANGIOGRAPHIC MORPHOLOGY

Under fluoroscopic guidance, specialized catheters are placed into the aorta to perform angiography of the ductus to further assess ductal shape and size. The different angiographic morphologies seen in veterinary medicine usually fall into the general classification scheme below as described by Miller et al. This helps us to confirm which device will be best suited for closure of the ductus. While most of these devices will work we do feel some work better with different ductal morphologies (Table 1).

Table 1. Types of Canine Patent Ductus Arteriosus

Type I	Type IIa	Type IIb	Type III
Narrow ductus with a constriction at the pulmonary ostium	Funnel shaped (wide aortic side) ductus that narrows toward to pulmonary ostium	Funnel shaped short ductus that narrows at the pulmonary ostium	Tubular shaped ductus with **NO Narrowing** at the pulmonary ostium

CATHETER-BASED THERAPY

Over the past 15 years the most commonly used device to accomplish this was the **Gianturco vascular occlusion coil** (Figure 1). Coil embolization was first described in veterinary medicine in the mid 1990s. Coils are made of a double helix stainless still wire with Dacron fibers attached, which induces clot formation within the ductus. Several techniques have been described for coil deployment into the ductus via transvenous or transarterial route. In typical cases, we use a modified myocardial bioptome transcatheter system, via the femoral artery, that allows controlled release of coils into the ductus using fluoroscopic guidance. This controlled release of the coil device reduced the risk of coils embolizing to the pulmonary artery or aorta. However, this system is limited to dogs large enough to accept this system within the femoral artery and has grown to be a somewhat expensive technique as the price of the bioptome used for this method has significantly increased. To expand our ability to occlude PDAs via transcatheter route, we have also described a coil free-release deployment protocol for dogs too small to have the bioptome system placed into their femoral artery. With this technique we have closed PDA in dogs as small as 0.7 kg in size. The main limitations to coil therapy are ductal diameter and morphology. Animals with large ductal diameter of the pulmonary ostium (ie, >3–4 mm) or type III ductal morphology were apt require multiple coils, experience incomplete closure or have coils embolized to the lungs. However, we have found high success using coils in small dogs with small-diameter PDAs or dogs large enough to be able to utilize a controlled release system. A number of other release techniques have also be described with a significant amount of success.

In our experience we found a similar to decreased complication rate utilizing coil techniques. Our overall complication rate of our first 100 coil attempts was approximately 7%, which was comparable to early surgery attempts here at Purdue University (9%). Complications included pulmonic and rarely (2 cases) aortic embolization of the coil, incomplete closure of the ductus, and in two cases death that we could directly attribute to the procedure. Also it on several occasions it would be necessary from multiple coils to be placed in a single or subsequent procedure which increased cost of the procedure and anesthetic times. Because the overall goal of any new, “less invasive” technique is or should be to improve upon the goal standard- surgical closure we felt coils were good but not good enough.

Thus, we came across the **Amplatz Vascular Plug** which is a self-expandable, cylindrical device made from a Nitinol wire mesh (Figure 2). It is securely attached to a threaded delivery cable which is unscrewed from the device when satisfactory placement is attained. This device was originally designed for arterial or venous embolization in the peripheral vasculature of human. The device size ranges from 4 to 16 mm in diameter. Use of this device for closure of PDA’s in veterinary medicine was first described by Purdue University Cardiology in 2005. The device comes in numerous sizes and is seated in the ampulla portion of the ductus causing physical obstruction until clot formation occurs. The device selected is typically 1.5 times the distal ductal

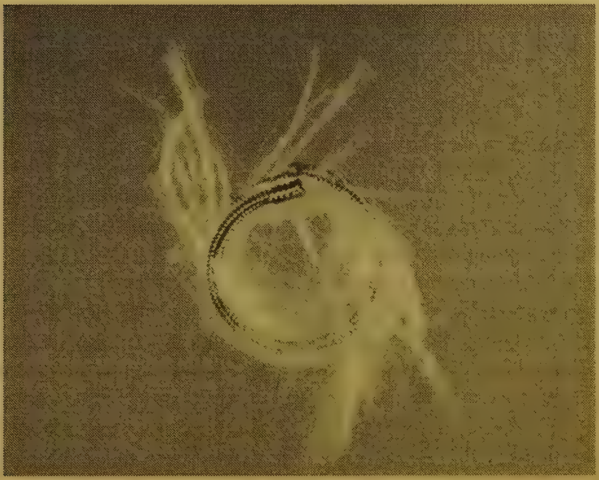

Figure 1. Gianturco vascular occlusion coil.

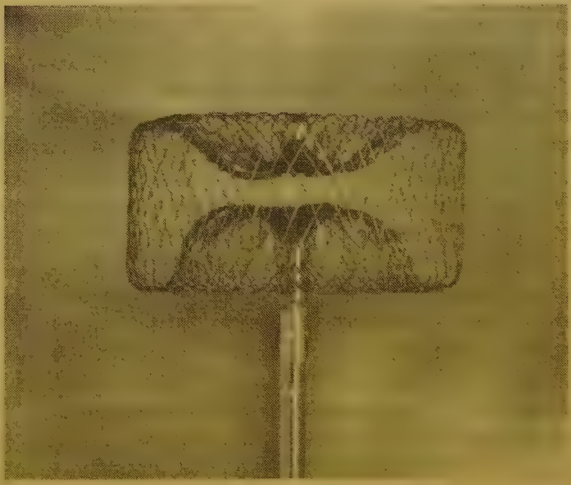

Figure 2. Amplatz Vascular Plug.

diameter. Often complete closure takes about anywhere from 5 to 15 minutes. In our experience this device is very successful as we have successfully obtained complete closure in approximately 98% of the cases in which we elected to use the PLUG device. We have experienced only one embolization of this device to the lungs in an early attempt to close a type III ductus. No subsequent negative affects were noted in this patient. No other "major" complications have been experience by our group when utilizing the plug. A minor complication, incomplete closure of the ductus has, occurred in only one case where we used an undersized device, less than 1.5 times the size of the distal ductal diameter. Currently, in our experience, it appears that this device is best suited for use in long tubular shaped PDAs such as Miller type I morphology. It appears to be limited in short type IIb PDAs as the length of the device may cause partial aortic deployment and also in type III PDAs as the diameter of these PDAs often exceeds the largest diameter device. One main large advantage of the plug is its ability to be deployed via the transvenous in addition to transarterial routes. In particular, this deployment route benefits small dogs with diminutive femoral access that also had "larger" PDA minimal diameters that would be best suited for a controlled release device. In these cases, we obtain venous access via the external jugular vein that typically allows large enough access to place the appropriate sized catheters through which a plug could be positioned into the ductus in retrograde approach. We have successfully used the transvenous route in 3/3 cases this was indicated.

The latest device used for closure of PDA is the **Amplatz Canine Duct Occluder (ACDO)** which is a self-expanding device made of a multi-layered nitinol wire mesh that was uniquely designed for closure of canine PDA's (Figure 3). Successful use of this device was first reported also in 2005 by University of Minnesota cardiology in 10 of 11 dogs. Uniquely, this device has a distal flat disk is that is placed on the pulmonary artery side of the ductal opening and a cup-shaped proximal portion that is deployed into the ductal ampulla. As the device is implanted, the proximal cupped portion conforms to the shape of the ductal ampulla with the waist of the device spanning the ductal pulmonary ostium to provide a secure fit. The device is detachable as it is preloaded onto a threaded delivery cable. The device can fit a number of sizes as it is available in 3-mm to 14-mm waist. We have enjoyed a 100% success rate with this device in 26 cases that we have elected to use it in. The shape of the cup portion of this device conforms nicely to the funnel shape of the ductal ampulla of type II PDA but this does not limit the devices use to that specific morphology. We have not attempted use in type III PDAs and based on its mechanism of security across the ostium it does not appear to be a suitable device for this morphology. The main limitation in our experience for those cases where the ACDO was indicated is that it can only be delivered via the transarterial route. Thus, it may not be amendable to use in very small dogs with larger than expected PDA diameters whose arterial access is too small to accept a 5 French catheter system (the smallest delivery system for this device).

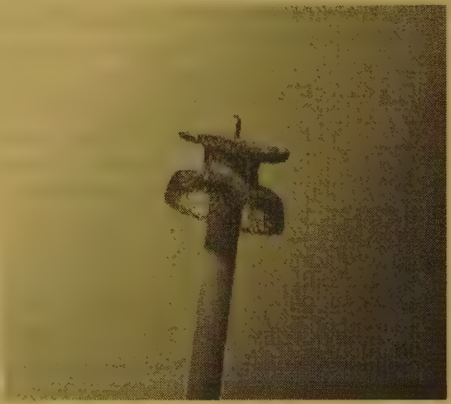

Figure 3. Amplatz Canine Duct Occluder.

While all three devices have some limitations we have had high success rates in utilizing all three devices. Overall, transcatheter PDA occlusion has the advantage that it is much less invasive than surgery. Although anesthetic time may be similar in some cases there is significantly reduced postoperative morbidity associated with transcatheter occlusion. This allows for much quicker recoveries as our patients usually are released from the hospital the day after the procedure barring any unforeseen complications. The concept of the ideal device that fits every circumstance for transcatheter closure of PDA is most likely an unrealistic one. More and more we are realizing that there is a role for all three devices and it is our practice to keep all three supplied and make the correct selection based on patient size, angiographic morphology of the patient's PDA, and the size of the pulmonary ostium or the distal ampulla. This gives our patient the best shot at having a successful transcatheter closure performed. For dogs with type III morphology, surgical closure remains the gold standard of therapy.

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FELINE CARDIOMYOPATHIES: WHAT DO WE DO FOR THERAPY OF THROMBOEMBOLIC COMPLICATION

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Thrombotic and thromboembolic complications have long been recognized as some of the most difficult to manage complications of feline myocardial disease. This syndrome is often referred to as feline aortic thromboembolism (FATE). Thrombosis represents clot formation within a cardiac chamber or vascular lumen. Thrombus formation has been historically linked to the presence of one of three predisposing factors known as *Virchow's triad*: 1) local vessel or tissue injury, 2) circulatory stasis, and 3) altered blood coagulability. These thrombi typically form in the left atrium, left ventricle or both. Embolization occurs when a clot fragment or other foreign material lodges within a distal vessel. Although the distal aorta is the most common site of embolization, various other organs (ie, the kidney, intestine) may become affected during embolic showers.

The prevalence of thromboembolism has been widely reported. In studies of FATE in necropsied cats, thromboembolism was seen in up to 48% of cats with hypertrophic cardiomyopathy (HCM), 29% with restrictive cardiomyopathy (RCM) and 25% with dilated cardiomyopathy (DCM). The prevalence in clinical settings obviously; is much less, being reported from a range of 12% in HCM cats to 18% in taurine deficient DCM cats. In recent clinical study FATE was seen in 0.57% of all feline clinical cases seen at a single referral institute. Incidentally, FATE is rarely seen in cats with hyperthyroidism; it has only been reported in 2% and 3% of cats in retrospective studies of cats with thyrotoxicosis.

CLINICAL PRESENTATION AND EVALUATION

The clinical presentation of cats suffering FATE may vary substantially depending on the location of the thrombus, the extent and duration of arterial occlusion, the degree of functional collateral circulation, whether the cat is suffering from concurrent congestive heart failure (CHF), and the development of other severe complications such as renal failure. Classically cats will present with paralysis, paresis, and painful; firm cold limbs and pale footpads, along with pale or cyanotic nail beds and potentially very weak to nonpalpable femoral pluses. Clinical signs are attributable to substantial tissue injury (ischemic neuropathy) due to the sudden arterial occlusion with almost instantaneous and complete interruption of blood flow, coupled with decreased collateral circulation secondary to vasoconstrictive substances being released from the thrombus.

If FATE is suspected based on clinical presentation, a minimum data base should include a complete blood count, coagulation and biochemical profiles; urinalysis, blood pressure, thoracic radiographs, electrocardiogram, and echocardiogram. Common clinical pathology abnormalities include elevated blood urea nitrogen (BUN) and creatinine, elevated serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) as well as increases in creatine phosphokinase (CPK). Hyperglycemia, and stress leukogram characterized by a mature neutrophilia and lymphopenia may also be present.

Thoracic radiographs are indicated to assess for cardiomegaly and CHF. Echocardiography gives a non-invasive assessment of cardiac structure and function. It also allows for investigation of the cardiac chambers for thrombi and spontaneous contrast (smoke) which is believed to result from blood stasis and subsequent rouleaux formation of red blood cells. Smoke may be present in the LA or LV and is a harbinger for thromboembolic potential.

MANAGEMENT OF FATE

Treatment of acute FATE should address general patient support; management of concomitant CHF and/or arrhythmias, and thrombus therapy to limit thrombus growth and formation. Chronic therapy is aimed at prevention of repeated thromboembolic events.

Analgesic therapy is essential for cats with FATE to alleviate pain, discomfort and stress associated with the ischemic myopathy during the first 24 to 48 hours following a thromboembolic event. Butorphanol, morphine, oxymorphone and fentanyl have all been used for this purpose. Maintenance of hydration, electrolyte balance and nutrition is also important during the first days of therapy. Thus it may be necessary to place nasoesophageal feeding tube, particularly when CHF has been resolved but there is persistent anorexia present.

Thrombolytic therapy with **streptokinase** and **urokinase** or with **tissue plasminogen activator (t-PA)** can be attempted within the first few hours of a thromboembolic event in attempt to lyse the clot and rapidly restore perfusion to affected limbs. Therapy with these agents has not gained as great of popularity in veterinary medicine as has been seen in human medicine. The expense associated with their use, the need for emergency availability and difficulty found in using these drugs as well as managing related complications in cats have all led to their minimal utilization veterinary medicine. We currently only use these drugs on rare occasions.

Anticoagulant therapy has been a mainstay of therapy for thromboembolic disease. Anticoagulants work by retarding the synthesis or accelerating the inactivation of clotting factors but they have no effect on established thrombi. Their use is therefore based on the premise of prevention of thrombus formation or preventing thrombus extension resulting in subsequent further reduction in arterial blood flow. **Coumarin (warfarin)** impairs hepatic vitamin K metabolism, thereby interfering with production of the procoagulant factors II, VII, IX and X Given the lack of evidence of preventing thromboembolism as well as the difficulty associated with monitoring these patients, and the potential for complications; wafarin therapy has not really gained favor in the treatment of this disease. **Heparin** has also been used as acute and chronic anticoagulant therapy in cats. Heparin also binds and inhibits von Willibrand factor thus exhibiting some direct antiplatelet effects. Classically unfractionated heparins (UFH) have been used for this purpose. **Low-molecular-weight heparins (LMWH)** are fractionated particles of heparin that are now available and have greater bioavailability, a longer plasma half life than UFH and can reportedly be given as a fixed subcutaneous dose once daily however most pharmacokinetic studies of this drug suggest the need for more frequent 2 to 3 times a day dosing. The problem with these studies however is the endpoint that was being studied prolongation of anti factor Xa has not been proven to necessarily correlate to preventing thrombus formation. Thus studies need to be performed that directly assess dosing affects on clot formation or prevention thereof.

Antiplatelet aggregating drugs are used to prevent the activation of platelets in response to exposure of blood to subendothelial connective tissue. **Aspirin** has traditionally been used in this manner as it induces a functional defect in platelets by irreversibly inactivating cyclo-oxygenase. Although aspirin should theoretically be beneficial, there is no evidence that aspirin is effective at preventing first time or recurrent thromboembolism. Also there is recent research that questions the ability of aspirin to decrease platelet stimulation and aggregation or to suppress overall thromboxane A_2 production. Current research with aspirin is focusing on the use of low dose aspirin (5 mg/cat every 72 hours) base of the theory of sparing endothelial prostaglandin I_2 synthesis. Newer antiplatelet drugs include the thienopyridine derivatives **ticlopidine** and **clopidogrel**. They function by irreversibly binding ADP to its receptor on platelets, thereby preventing the transformation of the IIb/IIIa glycoprotein receptor to its active form. Clopidogrel, however, effectively inhibited platelet aggregation with no apparent gastrointestinal side effects when dosed at 18.75 to 75 mg/cat/day PO. Current trials with clopidogrel are ongoing at Purdue University to assess drug efficacy versus aspirin in the FATCAT study.

SO WHAT DO WE DO WITH OUR PATIENTS?

Acute Stage

Supportive care is the mainstay of our treatment: Pain management and control signs of congestive heat failure – if present. Owners are offered the option of thrombolytic therapy.

A loading dose of clopidogrel 75 mg is given if the blood work is relatively normal along with a loading dose of unfractionated or low-molecular-weight heparin.

Chronic Stage

Depending on the cat's status (to be discussed further), chronically we recommend clopidogrel (Plavix®), 18.75 mg PO every 24 hours. We also commonly will use chronic therapy with LMWH. We commonly utilize these drugs in combination as they could offer synergistic effects of preventing clot formation. In such cases, we often use dalteparin 100 UI/kg every 12 hours or enoxaparin 1 to 1.5 mg/kg every 12 hours SQ.

Preventative

Cats that appear to be at risk for FATE (ie, thrombus, or spontaneous contrast of those with large diameter LA are seen on echocardiogram) we suggest starting therapy with clopidogrel (Plavix®) 18.75 mg PO every 24 hours.

OUTCOMES

Honestly, we do not truly have a handle on outcomes of these patients. We know poor prognostic indicators include hypothermia on presentation in the acute stage, thrombus present in the LA, and signs of renal dysfunction along with congestive heart failure. Historically most studies assessing survival of acute episodes report a 33% to 39% rate of survival to discharge. These numbers may be skewed significantly since this represents data mostly from referral institutions where cases may be significantly more severely affected. More recent data suggest improved survival rates with up to 73% of cats being discharged after acute events. Because prospective, double-blinded, placebo-controlled trials evaluating secondary prevention of CE are lacking, specific conclusions regarding efficacy of individual antithrombotic agents cannot be made. The Feline Arterial Thromboembolism; Clopidogrel vs. Aspirin Trial (**FAT CAT**) was designed to be the first prospective study to evaluate antithrombotic therapy for the secondary prevention of CE in cats. This study will hopefully give us some idea further insight into outcomes with this tragic disease and research efforts on the causes and prevention of thromboembolic disease may help to improve the survival figures in cats with cardiomyopathy.

References are available from the author upon request.

FELINE SYSTEMIC HYPERTENSION: DIAGNOSIS AND TREATMENT

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It has become increasingly apparent that systemic hypertension affects a large number of cats, resulting in significant clinical disease. It is important to be able to determine when systemic hypertension is present so appropriate therapy can be instituted to reduce or prevent severe consequences. Techniques are constantly being refined to measure blood pressure, as is our understanding of what "normal" blood pressure is in cats.

ETIOLOGY AND PATHOPHYSIOLOGY:

Cardiac output (CO) and systemic vascular resistance (svr) are both important in determining arterial blood pressure (MAP = CO X svr). Cardiac output itself is further determined by stroke volume (SV) and heart rate (HR) (CO= SV x HR). Thus, any disease state that affects CO, HR, SV or svr can result in systemic hypertension. Increased sympathetic tone and hyperthyroidism are common causes of increased heart rate. Stroke volume is increased with plasma volume expansion secondary to activation of the renin-angiotensin-aldosterone system (RAAS), increased dietary sodium, and increased arginine vasopressin (ADH). Increased svr is associated with increased RAAS, sympathetic nervous system (SNS), ADH, endothelin (ET-1), reduced nitric oxide (NO) production, and microangiopathic diseases (diabetes mellitus) or as a common pathway as a vascular response to continued elevated blood pressure.

While the most common cause in people is considered "essential" or idiopathic, this should not infer that there is no underlying cause. In people essential hypertension is often associated with some form of renal disease that results retention of sodium and water, alterations in the RAAS, SNS hyperactivity, Atrial natriuretic peptide (ANP) resistance, reduced clearance of vasoactive substances and reduced production of vasodilating substances (ie, NO or prostaglandins). In people, two principal theories for sodium and water retention with renal disease are: 1) resetting of the pressure-natriuresis relationship such that it takes a greater elevation in renal afferent arterial pressure to get the same degree of sodium excretion or 2) the nephron heterogeneity or ischemic nephron theory which states that there is a heterogenous population of ischemic and nonischemic nephrons. The ischemic nephrons have in creased renin release that induces increased sodium and water retention from the nonischemic nephrons thereby causing an increase in vascular volume and because there are only a small number of ischemic nephrons there is not a detectable increase in renin concentration within the systemic circulation. While these and a number of other theories abound and there have been billions of dollars spent in research in people the exact mechanism continues to elude researchers.

In cats, systemic hypertension is most commonly associated with chronic renal disease and hyperthyroidism with a reported incidence of 60 % to 69% in chronic renal disease and 80% to 89% in hyperthyroidism. There is much less known about the association of chronic renal disease and systemic hypertension association in cats compared with human medicine. Other known relationships include primary hyperaldosteronism, acromegaly, diabetes mellitus, and unknown. In most causes however, the diagnosis of systemic hypertension is only made once there is significant elevation and related severe clinical signs.

CLINICAL CONSEQUENCES

Organs that have an abundant arterial and arteriolar supply tend to have the most notable consequences of systemic hypertension theses include the brain, eye, kidneys and the heart. The vascular responds to chronically elevated pressures by smooth muscle hypertrophy within the medial layer to cause reduction in wall stress. If the increased pressure does not subside however, the vascular walls become fatigued and elastin molecules fracture, develop fibrous metaplasia and leak plasma resulting in hyalinization with resultant smooth muscle necrosis. This eventually results in reduced vascular compliance, which is a long lasting affect and can be irreversible forming the final common pathway for uncontrolled systemic hypertension.

Ophthalmologic Effects

Retinal blood flow is strongly controlled by autoregulation. Prolonged exposure to elevated systemic pressures results in leakage of blood and plasma causing retinal edema, retinal hemorrhage and accumulation of fluid in the subretinal space with subsequent retinal detachment. The choroidal vascular bed appears to be primarily affected by hypertension in cats. Damage to this vascular bed results in necrosis and atrophy of the retinal pigmented epithelium and ischemia to the outer retinal layer. These alterations are responsible for the high incidence of complete retinal detachment seen with cats affected with systemic hypertension.

While acute blindness is the most common clinical sign associated with hypertensive retinopathy in cats, this occurs very late in the course of the disease with more subtle signs missed by the owner. Common ophthalmologic findings include retinal vessel tortuosity, retinal hemorrhages, blood within the vitreous humor, hyphema and focal or complete retinal detachment. While complete retinal detachment is still associated with a poor to guarded prognosis, there are some cats that regained vision after successful antihypertensive treatment.

Central Nervous System (Brain)

Cerebral blood flow is determined by systemic pressure and is also under autoregulatory control of the arteriolar beds. The beds vasoconstrict or dilate in response to elevated or decreased systemic pressures respectively to maintain a relatively constant cerebral blood flow. Constant vasoconstriction of these vessels results in fibrinoid necrosis that can lead to decreases in blood flow, thrombosis, and ischemia, loss of vascular integrity, hemorrhage, edema and infarction. Clinical signs can include depression, dementia, stupor, and seizures. Acute hemorrhage or edema can results in rapid clinical deterioration.

Renal

Renal flow just like those above is also under autoregulatory control with a very constant range by the renal afferent arterioles. Chronic elevation of systemic pressures outside of the normal operating range of autoregulation results in damage to the afferent arteriole. This results in a less responsive arteriole to alterations in systemic pressures that dilates and leads to progressive glomerular hypertension and renal injury. As in humans, it has been well documented that uncontrolled systemic hypertension is associated with progressive renal disease; therefore, it is often difficult if not impossible to determine where an individual patient falls within the vicious cycle.

Cardiovascular

Elevated systemic pressures result in increased left ventricular afterload and wall stress. The myocardial response to this abnormal pressure is concentric hypertrophy, which is an attempt to bring the left ventricular wall stress back to a normal despite the elevated afterload. Although the wall stress returns to normal, there is an increase in cardiac work and oxygen demand by the myocardium. The hypertrophy of the myocardium is accompanied by remodeling of the interstitium characterized by excessive collagen production that is theoretically under the control of angiotensin II, aldosterone, transforming growth factor-β, platelet derived growth factor, tumor necrosis factor α , interleukins-1 and -6, and others. The increased fibrosis results in loss of ventricular compliance and forms the basis of diastolic heart failure.

The vascular changes (medial hypertrophy, fibrous metaplasia, hyalinization, edema, necrosis and sclerosis) occur are seen in most vascular beds. In addition, the coronary flow is also affected and results in less vasodilatory capability reducing coronary flow reserve. The increased workload combined with the reduced ventricular compliance and reduced coronary reserve results in altered myocardial oxygen demand/oxygen supply relationship that increases the risk for myocardial ischemia, infarction, arrhythmias, heart failure and sudden death.

Clinical findings related to the cardiovascular system are common in cats with systemic hypertension. Cardiomegaly and tortuous aortic arch can be seen in thoracic radiographs along with the pattern of left anterior fascicular block on surface electrocardiography however, these are not specific to systemic hypertension. Echocardiography often shows mild to moderate left ventricular concentric hypertrophy with minimal left atrial changes. Congestive heart failure secondary to systemic hypertension appears to be very rare in this author's experience unless concurrent cardiac disease is present.

DIAGNOSIS

Measurement of blood pressure can be done one of two ways. One direct measure by inserting a needle or catheter into the arterial system is the "Gold Standard." While this is a very accurate and simple method, it does require specialized equipment, experience and is not practical for repetitive measurements that are necessary for monitoring. Because of these limitations the indirect method of blood pressure measurement has become the most accepted and widely used method on a daily basis. There are three methods commonly used to measure blood pressure indirectly; Doppler, oscillometric and photoplethysmographic.

Doppler

This method utilizes Doppler shift principles of sound. Essentially, as the moving blood passes the piezoelectric crystal of the unit a sound is generated. The crystal should be placed over a peripheral artery (dorsal pedal, palmar or plantar) or the base of the tail to achieve a good audible signal. A pressure cuff is then wrapped around the limb proximal to the crystal and inflated until the signal of blood flow is lost. Pressure is then slowly released from the cuff until the audible signal of blood flow is just heard. The pressure reading at the point where the audible signal becomes apparent again is the systolic pressure. The Doppler technique is only able to accurately measure systolic pressure. The diastolic pressure can be estimated by the sound of change as the pressure continues to drop but this is very inaccurate. This has been the best technique for cats. There are a number of newer devices that are challenging this belief.

Oscillometric

The oscillometric method evaluates the oscillation in an air bladder (cuff) to measure blood pressure. Only the systolic pressure is truly measured. Both the diastolic and mean pressures are calculated values. These machines will also record pulse rate. The cuffs have an arrow indicator that should be placed over the artery that is to be used. Most machines are automated and the simple push of a button is all that is needed. While these units have historically performed better in dogs and larger animals there are some that have shown better function in cats although in this author's opinion Doppler techniques still remain best suited for cats.

Photoplethysmography

This commonly used method in human medicine is rarely used in veterinary medicine despite one study stating it accuracy and reproducibility. With this technique, the change in density of the blood circulating in the capillary beds beneath the skin is detected by infrared light. Calculations are made based on these changes so systolic, diastolic and mean pressures can be recorded. Additionally pressure waveforms are generated that can be displayed on the monitor.

Regardless of the technique used, certain steps should be followed in order to improve the accuracy of your blood pressure reading. The readings should be taken one the cat is in relatively calm state and away from loud noises, other animals and distractions. The artery should be at the same height as the heart and the width of the cuff should be about 40% of the circumference of the limb. Because of the well recognized 'white coat effect' on blood pressure, measurements should be repeated from 3 to 10 times with the average of these readings used as the recorded measurement. For purposes as a guided, this author recommends the following example of pressure assessment: We typically consider a pressure of 170 mmHg to be normal in a cat in the clinical setting. If a cat has a systolic pressure of 190 mmHg and the above steps have been taken, then we consider this cat to have systemic hypertension. If a cat has a pressure reading between 170 and 190 mmHg and has clinical signs (renal insufficiency, retinal lesions, neurologic signs) then we consider that cat hypertensive and suggest treatment. If no clinical signs are present, we suggest close, frequent monitoring of blood pressure for this patient.

Cats diagnosed as hypertensive should have extensive exams for the underlying cause of the hypertension since majority of hypertensive cases are secondary in nature. Cats should have renal function and electrolytes evaluated as well as thyroid status. Ophthalmic exams should also be performed on all suspects.

TREATMENT

Concurrent treatment of underlying causes is a critical component to successful control of blood pressure. Hyperthyroid cats should receive antithyroid treatment along with an antihypertensive drug. Chronic diseases such as renal disease and diabetes mellitus should be adequately treated. Failure to provide such concurrent treatment will often result in inadequate pressure control. Prolonged antihypertensive therapy may be necessary even after reversible causes of hypertension (ie, hyperthyroidism or primary aldosteronism) have been treated due to the small vessel disease that develops with chronic hypertension.

Vasodilators

Currently these agents are the mainstay of hypertensive therapy in cats. Their use results in precapillary arteriolar dilation thereby reducing systemic pressures. The two main classed of vasodilation agents used in cats are the dihydropyridine calcium channel blockers (CCB) and the angiotensin converting enzyme inhibitors (ACE-I).

Dihydropyridine Class of Calcium Channel Blockers (CCBs)

These drugs induce significant arteriolar smooth muscle relaxations with little central (heart) electrophysiologic effects. These are potent arterial vasodilators and have been proven to be very effective in feline hypertension from any cause. There is often concern that these agents may predispose the kidney to glomerular hypertension due to renal afferent arteriolar vasodilation. However, the concurrent reduction in systemic pressures may counterbalance this effect and in human studies results demonstrate equivalent reduction in Proteinuria when compared to ACE-Is. The CCBs are currently our first choice for feline hypertensive patients.

- **Amlodipine** (Norvasc®) – 0.0625 mg/cat PO q 24 hrs (< 5 kg)
    - o 0.125 mg/cat PO q 24 hrs (> 5 kg)

Angiotensin Converting Enzyme Inhibitors (ACE-I)

These agents reduce the amount of angiotensin II (ANGII) produced through RAAS. Angiotensin II induces sodium and water retention and is a potent vasoconstrictor. These agents have been very effective in human patients and have displayed renoprotective properties and they are recommended with clinically significant proteinuria. Unfortunately, these agents seem to have limited effectiveness in treating hypertensive cats for two main reasons: 1) RAAS does not appear significantly elevated in chronic renal disease or hyperthyroidism and 2) cats (and dogs) are generally less responsive to the vasoactive properties of the ACE-I when compared with humans. Thus, this class is usually our second choice:

- **Enalapril** (Vasotec®, Enacard®) – 0.25–0.5 mg/kg PO q 24-12 hrs
- **Benazepril** (Lotensin®) -- 0.25–1 mg/kg PO q 24 hrs

For any undergoing treatment for hypertension, frequent indirect monitoring is essential. This should be weekly or biweekly until goal pressures of 120 to 170 mmHg are attained. Other common additional protocols such as timing and use of α-receptor (prasozin) and β-receptor blockers and the potential role of diuretics will also be discussed.

Feline systemic hypertension is s common clinical disease that needs to be monitored for and its prevalence and devastating consequences should increase the use of blood pressure monitoring equipment in all veterinary practices.

References are available from the author upon request.

NEW TEST FOR FELINE CARDIOMYOPATHIES

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The prospect of biochemical screening of cats for heart disease is a very attractive prospect. This is a very exciting endeavor in that it could allow individuals without extensive training in cardiology and echocardiography to identify animals with heart disease more accurately and at an earlier point in the disease process. If successful such testing could allow for the delivery of early treatment and aid in the clarification of equivocal test results. The ability to screen cats for the potential of heart disease may also be especially helpful to detect those cats at risk for heart failure when anesthesia or fluid therapy is indicated which often results in the development of congestive heart failure.

While the prospect of biochemical testing is an exciting one, filled with possibilities we must be careful in how these test which will likely become available at some point, is used. One it should be recognized that these test most likely will be used as an aid to identify those who need further advanced testing and not a replacement for advanced testing. Also we must identify test for screening that has a very high sensitivity and at least a reasonable level of specificity (i.e. it should detect at least 90% of the target group and likely a specificity of 70%).

POTENTIAL TARGETS

Cardiac Troponins

The cardiac troponin complex is composed of three subunits (I, T, and C) that regulate the excitation-contraction coupling of the sarcomeric proteins. Injury to cardiac muscle induces release of these subunits into the circulation where their levels are proportional to the severity of myocardial damage. In humans cardiac troponin I (cTnI) concentrations are used to assess the risk of complications in patients with myocardial ischemia, myocarditis, arrhythmia, critical illness, cardiac contusion, and congestive heart failure. Measurement of circulating cTnI have been shown to be more sensitive means of detecting myocardial cell injury than measurement of either plasma cardiac troponin T or serum creatine kinase isoenzyme in cats after blunt thoracic injury.

The final value of measuring circulating troponin concentrations in cats with hypertrophic cardiomyopathy (HCM) is not well established. There have been several studies that have proven an increase in circulating troponin levels in HCM cats. Sleeper et al have published normal values for circulating plasma troponin I concentrations in cats. Schober et al found elevated troponin concentrations in cats with cardiomyopathy. Connolly et al showed increase in cTnI cats compared with normal cats and found statistically significant but weak correlation of cTnI serum concentration to the thickness of the left ventricular free wall but not with the interventricular septum on echocardiogram. Overall their assay revealed 87% sensitivity and 84% specificity. Herndon *et al* revealed similar results of increased cTnI levels in HCM cats compared with a normal population. Herndon's also displayed 85% sensitivity and 97 % specificity. These results are somewhat limited by the fact the several of the 'normal' cats had not had an echocardiogram performed. Also this study only studied pre-selected cats with moderate to severe HCM thus the results may be of limited value in cats with mild disease and the positive predictive value may also be limited by the fact the no other populations (ie, cats with concurrent disease or other forms of cardiac disease) were study.

So while the potential for using cardiac troponins may be high there is sill a number of other studies that need to be performed prior to its utilization as a screening tool for cats with HCM. Assessment of cats with other diseases or other forms of cardiac disease may be useful. Also assessing larger populations of consecutive cats will also be useful in helping determine whether this test will be of value as a screening tool.

Natriuretic Peptides

Atrial and brain natriuretic peptides (ANP and BNP, respectively) are small peptides that are released from the heart that counter the negative effects of angiotensin II and sympathetic activation. ANP is a 28 amino acid peptide secreted from the atria in response to atrial stretch. It is secreted as a propeptide that is cleaved into the biologically active 28-amino-acid C-terminal ANP and the 98-amino acid N-terminal (NT)-proANP that are secreted into circulation in equimolar quantities. The N-terminal portion however has a longer half-life in circulation and is more easily measured. BNP on the other hand is secreted primarily from the ventricles (although there is some atrial release of this peptide) due to increases stress on individual myocytes. It is a 32-amino acid peptide that shares structural and biological similarities to ANP. Both ANP and BNP bind to the natriuretic peptide A receptor which mediates natriuresis, vasodilation, renin inhibition, antimitogenesis, and lusitropic effects in the heart. Both peptides are cleared via the natriuretic peptide-C receptor and degraded by neutral endopeptidase.

Circulating levels of ANP and BNP have become known as an important diagnostic test and prognostic marker for congestive heart failure in human cardiac patients. In veterinary medicine small studies have shown increased levels of BNP and ANP along with several other hormones in dogs with congestive heart failure compared with dogs with heart disease and no heart failure. Prosek *et al.* reported increased circulating levels of BNP in dogs with congestive heart failure compared to dogs with respiratory induced dyspnea. Biondo *et al.* reported increased immunohistochemical staining for ANP and BNP in four cats with HCM compared with normal cats. HCM cats showed increased and more diffuse staining pattern for ANP and BNP in the atria and only found BNP in the ventricles of HCM cats compared with normal cats. There have been no studies that describe increased circulating BNP for cats with HCM compared to normal cats that this author could find.

Recently however a new test for screening cats for heart disease was advertised and released to test for NT-pro BNP levels. This test is available through Veterinary Diagnostics Institute and is called the Vetsign Feline Cardio SCREEN NT-proBNP test. The results from a study controlled by the Royal Veterinary College of 80 compared 28 normal cats and 52 abnormal cats. Results of this study show low BNP levels in normal cats and elevated levels in asymptomatic cats with heart disease. However, from the results shown there were only 9 cats in this subgroup and there was some overlap between this group and the normal group. There was a clearly significant difference between the normal group and the cats with symptomatic heart disease (heart failure cats). Caution should be taken when assessing these results and this cardiologist strongly recommend restraint at utilizing this test as a screening test as only 9 cats were utilized in this study and this data to my knowledge has not be published in peer reviewed fashion. Where this test appears to be useful is in distinguishing cardiac-related dyspnea versus other causes. However, delay in obtaining results may make this obsolete in practical use at this time. Currently none of these results could be found in peer-reviewed articles. Again, while the prospects of having such a test is very exciting, caution must be taken in utilizing this test based on the current results given by the company to utilize this test as a tool for screening cats for heart disease. Further studies need to be performed to prove the usefulness of this test in such a manner.

Endothelin

Endothelin (ET-1) is a potent 21 amino acid vasoconstricting peptide produced by the vascular endothelium and the heart. It is converted from a 38-39 amino acid peptide by the action of endothelin converting enzyme (ECE). Elevations in ET-1 in heart failure patients have been reported in people and in dogs. In people these levels have been found to have significant correlations with the degree of functional impairment. Prosek et al reported plasma endothelin immunoreactivity in healthy cats and cats with cardiomyopathy. Plasma ET-1 mean (95% CI) concentrations were 0.777 (0.6536–0.924) fmol/mL in the control cats, 1.427 (0.922–2.209) fmol/mL in 12 asymptomatic cats with cardiomyopathy but and 2.360 (1.666–3.343) fmol/mL in 16 cats with cardiomyopathy (HCM = 8, RCM/UCM = 7, DCM = 1) and CHF (n = 15) or STE (n = 4). Plasma immunoreactivity of ET-1 was significantly higher in asymptomatic cats with myocardial disease versus normal cats and in symptomatic cats with myocardial disease with versus normal cats. Once again small sample size and overlap in the normal and asymptomatic affected cats limits this test's ability to be used a screening tool.

Genetic Testing

Currently in Maine Coon cats with HCM, Meurs et al have identified causative mutations several sarcomeric genes, including the myosin binding protein C (MYBPC3) gene. Reductions in the protein in myocardium from affected cats in comparison to control cats were found by this group. They identified a single base pair change (G to C) in the feline MYBPC3 gene in affected cats that altered the protein conformation of this gene and resulted in sarcomeric disorganization. Currently testing is still currently being performed and evaluation of this test as a screening tool is ongoing. In this authors experience we have found mixed results when comparing genetic testing results with echocardiographic results. Opinions have to be conserved at this time because a single negative echocardiographic result for HCM on cats that test positive for the mutation may not be predictive for future disease in these cats. While these are very exciting and intriguing test one must also realized that this has only been assessed in Maine Coon familial HCM and can not be applied to other cat breeds at current time. This, however, is a huge start in the utilization of DNA technology is assessing this disease in all cats.

SUMMARY

The prospect of being able to screen cats for heart disease utilizing biochemical testing is very exciting. This can be utilized to help guide owners in seeking further more expensive and time consuming testing (ie, echocardiography and specialist evaluation) and in identifying asymptomatic cats who might be at risk for developing congestive heart failure (CHF) if placed under anesthesia or given fluid therapy. Currently the status of such test is questionable at best for use in this manner. Most results suggest that these tests may be best utilized for differentiating cardiac dyspnea from other causes of dyspnea. However, given the methodology of running these test, the limited scope of available labs that run these test and the length of test turnaround, utilization of these test to decide which systems to work up may be obsolete and other test may be more useful given the urgency of need. Further studies need to be performed and test modifications validated for use prior to being able to use these test in an efficient manner. It is feasible given the progress thus far that these goals could be accomplished in the near future and give newer technologies and the advancement of proteomics as a field of interest new more sensitive and specific proteins may be found to be utilized for screening our cardiac patients.

References are available from the author upon request.

CLINICAL CARDIOLOGY UPDATE: CONGESTIVE HEART FAILURE THERAPY

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There are many different diseases that can cause signs of congestive heart failure (CHF); thus there are numerous approaches one can take for therapy depending on the patient's particular circumstance(s). There is a heavy reliance on medical management to control clinical signs of heart failure. The ultimate goal of which is to improve the patient's **quality** and potentially length of life generally accomplished by reducing retention of salt and water, improving cardiac function and reducing cardiac workload. Owners must be made aware of this goal as there are very few of curable diseases that cause congestive heart failure.

Specific treatment decisions are made possible by an accurate diagnosis of primary cause of the clinical signs (systolic or diastolic pump failure). Other considerations include, the timing of the clinical signs (acute vs. chronic HF), the severity of disease (mild, moderate, or severe HF), and the predominant manifestation of clinical signs (ie, left vs. right heart failure and congestive vs. low-output failure).

In recent years, there has been a greater understanding and appreciation for the role of neuroendocrine system changes in heart failure. With this understanding came a new focus on therapy, not concentrating specifically on symptomatic relief but attempting to slow or possibly stop the progression of disease. Improvement in clinical signs of disease is simply a consequence of modification of these changes. This approach appears to be of primary importance and therapeutic considerations include how disease states affect activation of these systems. Current therapeutic options are facilitated not only by knowledge of pharmacology, hemodynamic effects of drugs, the nature and prevalence of drug side effects, drug efficacy, and the effects of drugs on quality of life but also how given drugs will alter neuroendocrine function.

These systems include but are not limited to the rennin-angiotensin-aldosterone system (RAAS), sympathetic nervous system (SNS), the natriuretic peptides, and arginine vasopressin (ADH). The RAAS system involves the generation of angiotensin II (ANG II) and aldosterone (ALD) in response to reduced renal perfusion, reduced sodium load to the distal convoluted tubule, and increased sympathetic tone. ANG II and ALD both cause increased sodium and water retention along with inducing significant myocardial and vascular smooth muscle remodeling and fibrosis. These latter effects represent irreversible changes and progression of disease. ANG II is also a potent direct vasoconstrictor which increases afterload. ALD has more of a permissive effect on maintaining vascular smooth muscle tone rather than inducing vasoconstriction. The prognosis for heart failure is inversely proportional to the degree of sympathetic nervous system activity. Increased sympathetic tone causes vasoconstriction, renin release, arginine vasopressin release (a potent vasoconstrictor and water retainer) and has been shown to induce myocardial and vascular smooth muscle remodeling and fibrosis. It has been proven that there is baroreceptor dysfunction in heart failure patients and it is felt that this plays the central role in increased sympathetic tone in these patients. Natriuretic peptides (ANP and BNP) are produced by the atria and ventricles in response to increased stretch induced by volume overload and increased pressure. They antagonize the vasoconstriction and sodium/water retention from other neuroendocrine actions and acts as the body's internal regulator. Unfortunately, it is not very effective as they are broken down rather quickly and their effects are essentially neutralized.

In veterinary medicine, alas there is very little data available to assist us in determining the optimal therapy for our patients with congestive heart failure (CHF). Given the abysmal prognosis associated with CHF, there is a need for better therapies or applications of those we have. To date, only data generated using the ACE inhibitors enalapril and benazepril and the positive inotrope pimobendan have been shown to improve the length and quality of life in the dog. Given the paucity of clinical data in veterinary patients, we have become reliant on data generated in human patients with similar disorders with a view to considering these data for our patients. Thus long-term multi-center trials need to be completed to optimize CHF therapy for veterinary patients.

MEDICAL MANAGEMENT

Diuretics are the most commonly drugs for patients with CHF. These drugs reduce the preload on the heart and thus reduce backward pressure on the venous system. Asymptomatic heart disease is usually not associated with measurable activation of certain neuroendocrine systems; however, these neuroendocrine responses are stimulated following diuretic therapy secondary to the decreased preload induced reduction of cardiac output. Because this stimulation of the neuroendocrine system is assumed to be counterproductive, most cardiologists do not recommend single agent use of furosemide for chronic treatment of heart failure. This does not mean that appropriate diuretics should not be used when congestion develops. The combined use of ACE inhibitors and diuretics compromises one of the kidneys' normal compensatory mechanisms (vasoconstriction of the efferent arteriole) and can lead to azotemia when excessive diuretic dose is initiated. While it is this author's experience that this is not a common occurrence, I strongly recommend assessing renal function if possible prior to onset of this therapy and adjusting therapy accordingly. We currently use the lowest possible dose of furosemide in animals with CHF. This often means a degree of experimentation must be performed to best evaluate an individual animal's needs. In most instances of mild CHF, canine patients are released from our hospital on 1 mg/kg q 12 PO q 12 hrs, and in most cats we initially try to use 6.25 mg/cat/day for chronic therapy. When a dose of 2.2 mg/kg twice to three times a day is exceeded during chronic therapy, a thiazide diuretic (hydrochlorothiazide) is "stacked" on to therapy as an opposed to further increase in furosemide dosing. At this level of dosing some degree of diuretic resistance has been reached the addition of a synergistic diuretic is often of great benefit to your patient. While others suggest utilizing spironolactone in this capacity we typically will not due to the minimal diuresis affects of this drug. Spironolactone has however gained a more constant place in therapy due to the additional benefit of aldosterone-antagonism, and has been shown to have survival benefits in human CHF studies. Thus we often will have spironolactone on board concurrently at the onset of therapy for the CHF patient. The dosing spironolactone to this end point in dogs is highly empirical as no study has been repeated to mimic that seen in humans although in numerous animal models this antifibrotic effect has been duly noted.

Angiotensin-converting enzyme inhibitors (ACE-I) are commonly used in the management of heart failure. Their benefits include reductions in plasma concentrations of angiotensin II and aldosterone; therefore, fluid retention and vasoconstriction are inhibited. ACE inhibition also is known to reduce the progressive cardiac enlargement and remodeling that attends most forms of heart failure.

Enalapril (0.5 mg/kg SID to BID) is the ACE inhibitor most frequently used for dogs in the United States. We standardly employ twice a day dosing for dogs and feel this is most appropriate to achieve benefits for CHF and has been safe in the absence of significant pre-existing renal disease or excessive concurrent diuretic use. Although enalapril is licensed for use only in dogs, its successful use has been described in cats with hypertrophic cardiomyopathy (HCM). Another ACE-I commonly used in the US is benazepril, 0.25–0.5 mg/kg PO q 24–12 hours (dogs) and 1.25 mg PO q 24 hours (cats).

Other direct-acting arteriolar vasodilators such as amlodipine or hydralazine may be very useful as disease progresses. While these drugs lack the favorable neuroendocrine effects that are associated with ACE-I, we often consider use of one of these (preferably amlodipine) patients with CHF resulting from mitral valve disease or those with significant mitral regurgitation secondary to annular dilation especially when standard therapy (discussed below) appear inadequate.

With myocardial failure (dilated cardiomyopathy, end-stage mitral regurgitation), positive inotropes play an integral role. Positive inotropes may also have a beneficial effect in early mitral regurgitation by reducing the severity of regurgitation through reduction in isovolumetric contraction time and geometrical changes on the mitral annulus. Pimobendan is a new cardiac medication which acts as a calcium-sensitizing agent to increase inotropy. Because the drug increases the sensitivity of the contractile elements to the existing calcium, there seem to be fewer deleterious effects than drugs that act by increasing calcium flux into the myocardium. Inhibition of phosphodiesterase also may account for some of the beneficial effects of pimobendan. There has been no documentation of increased mortality in dogs treated with pimobendan and improvements in clinical signs may result in longer survival for dogs as quality of life impacts an owner's decision to euthanize the dog. This will be determined as more study results are released on this drug. The dose of pimobendan for dogs is 0.25 mg/kg q 12 hrs. The dose for cats (those with systolic dysfunction) has been proposed to be 1.25 mg/cat q 12 hours but there is very limited experience with this drug in cats.

The use of digoxin in heart failure has been debated for hundreds of years. It is certainly recognized as a drug with beneficial effects but with a significant risk for toxicity. There is no argument against its use with atrial fibrillation but some controversy still exists about its use with normal sinus rhythm especially in human medicine. The arguments for using digoxin include its positive inotropic effect, as well as restoration of blunted baroreceptor responses and reduction of excessive sympathetic tone which is important in the neuroendocrine based treatment of CHF. In a large trial in people with heart failure, digitalis did not impact mortality, but did reduce the need for hospitalization. Those who are not enthusiastic users of digoxin point out that the drug has significant potential for toxicity, that it can be difficult to dose in veterinary patients, and that it has not been documented to improve survival. This author has not experience such frequent difficulties with toxicities or dosing. We historically employed digoxin as the third wing of triple therapy for CHF however since the FDA approval of pimobendan we employ ACE inhibitors, pimobendan, and diuretics for the early stages of CHF, and add digoxin when significant supraventricular arrhythmias (ie, atrial fibrillation), recurrent syncope, or advancing CHF requires additional therapies.

Beta-blockers (propranolol and atenolol) have been used for many years in cats with HCM. While there benefit in this disease is under fire at the moment, more recently, beta blockade has gained favor in dogs as a therapeutic modality for treatment of heart failure. Many human studies on the use of beta blockers (ie, metoprolol, carvedilol) have documented the benefits of chronic treatment with beta-blockers. These effects are often not seen for several months after initiation of beta blockade. Such benefits include up regulation of previously down regulated beta-receptors, improved cardiac performance (improved stroke volume), and improved survival. Because beta-blockers have negative inotropes and chronotropes effects, it is this author's opinion that they may be best employed in animals that are minimally symptomatic with early/mild heart failure where long-term favorable affects (if present) on mortality and hemodynamics may take place with minimal risk of resultant decompensation of the patient.

Finally, one should not leave out the affects of nutrition for treatment of heart disease. Very interesting data have been revealed to show the affects not only of adding low-salt diets to therapeutic regimes but also fish oils that contain n-3 fatty acids help to reduce to production of cytokines and other inflammatory mediators in both people and dogs.

CONCLUSION

It is currently believe the maladaptive neuroendocrine responses play a very important role in the pathogenesis of heart failure. While traditional treatments such as diuretics remain important, most aspects of current management are directed toward blunting of the body's neuroendocrine responses even through dietary modification.

References are available from the author upon request.

DIAGNOSIS AND TREATMENT OF SYNCOPE

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Syncope is the sudden temporary loss of consciousness that is associated with loss of postural tone as a result of an abrupt decrease in cerebral perfusion or decreased delivery of essential nutrients (ie, glucose) to the brain. The true incidence of syncope is unknown; however, it has been reported to occur in a referral database in 0.15% of dogs and 0.03% of cats. This number may be due to the fact that 1) it is a referral database and 2) that often to both the trained and untrained eye it may be difficult to distinguish syncope from seizure activity.

During a syncopal event, animals will usually collapse into lateral recumbency and may have concurrent stiffening of the limbs, opisthotonous, urination and vocalization. However, it is uncommon to see persistent facial fits, persistent tonic/clonic motion, defecation, postictal dementia, and neurologic deficits with cardiovascular mediated syncope. What may often confuse one who witnesses a syncopal event is that on occasion some animals may have "convulsive syncopal episodes" (CSE) that results from severe hypotension or asystole. Typically CSE are preceded by loss of muscle tone whereas seizure activity is usually preceded by atypical limb or facial movement or even staring spells prior to the loss of body tone.

ETIOLOGY AND PATHOPHYSIOLOGY

The mechanisms underlying syncope are usually rather acute in nature. These mechanisms usually involve reduced cardiac output resulting from arrhythmias or decreased cardiac filling, obstruction of blood flow from the heart, hypoxia or hypoglycemia (with normal cerebral flow) or severe decreased vascular resistance related to neurocardiogenic reflexes. There are numerous diseases that can result in any one or a combination of these mechanisms. A partial list is presented in Table 1.

The vast majority of syncopal events in veterinary medicine are due to a transient reduction in brain blood flow. A sudden decrease in cardiac output (CO) or vascular resistance reduces mean arterial pressure may both result in reduction of cerebral blood flow. The most common causes we see in our patients are cardiogenic in nature. Two thirds of dogs and cats with syncope also have a cardiac disease. Most of these are related to rhythm disturbances which are secondary to inherent cardiac disease. Underlying cardiac functional or structural abnormalities exacerbate the negative effect of arrhythmias on cardiac output. Poor myocardial contractility, impaired filling as with pericardial disease or outflow obstructions can all result in an inability of the heart to maintain sufficient cardiac output to meet increased demand during excitable states, even under normal cardiac rhythms.

Non-cardiogenic diseases such as those that result in increased intracranial pressure can result in syncope also by reducing cerebral perfusion pressure by compressing intracranial vessels. While the majority of animals with severe hypoglycemia will present with weakness or seizures, a fair number may present with syncope or CVE while maintaining normal cardiac output. Hypoxia as a result of right to left shunts, severe acute anemia or pulmonary disease can result in insufficient cerebral oxygen delivery and syncope.

Another common occurrence that we see is cough (tussives) syncope. Some like to use the term 'cough drop' to describe syncope induced in this manner. This form of situational syncope occurs most often in brachycephalic dogs; however, it is also common in dogs with airway disease, tracheal collapse, or those with severe left atrial (LA) enlargement causing compression of the left mainstem bronchus. Coughing results in increased intrathoracic pressure, which decreases venous return (preload) and cardiac output. It also decreases intracranial pressures both of which may cause a decease in cerebral perfusion if severe enough coughing occurs. Coughing may also induce reflexive bradycardia by stimulation of the vagal nerve.

Neurocardiogenic (vasovagal) reflex resulting in syncope is less common in animals than in people however there are reports of syncope that occurs secondary to sudden bradycardia following bouts of tachycardia, especially in small breed dogs with advanced valvular disease. In cases of neurocardiogenic syncope, acute sympathetic activity (induced by excitement) provokes a strong reflex vagal response that results in bradycardia. Ventricular mechanoreceptors play a huge role in this reflex in that their activation due to forceful contraction results in a surge in afferent neural traffic stimulating paradoxical brainstem response to vagal activation.

APPROACH TO THE PATIENT WITH SYNCOPE

Clues as to the underlying cause of the episodes can be elicited through a thorough history and physical examination of the animal. Getting a detailed (almost dramatic) description of the events as they occurred as well as the preceding events, prodromal signs, and the animal's mentation and behavior prior to and after the event can help in differentiating cardiovascular syncope from seizure activity and other causes of collapse. In a nice human prospective study the etiology of the syncopal event was able to be correctly elicited in 32% of patients based on obtaining a thorough history and physical examination. Performing diagnostic testing in a stepwise manner is critical in diagnosing the syncopal patient.

Some questions you should consider asking when obtaining a history include:

- What was the animal doing immediately prior to the event?
- How long did the event last?

- Did the animal lose consciousness during the event?
- Did the animal have muscle (motor activity) movement during the event?
- If not; did the muscles appear stiff or relaxed?
- Did the animal urinate or defecate?
- Was the animal normal after the event or disoriented and confused and if so for how long after.
- Current medications.
- Any possible exposure to toxins?
- Have there been any changes in behavior recently?
- Was there any vomiting or coughing prior to the event?

While this is not an all inclusive list of questions and the answers may take you down different lines of questioning, answers to most of these questions may help you decide to follow the path of seizure or syncope for you next steps in diagnostic testing.

Routine database of CBC, biochemical profile, urinalysis, heartworm test, and arterial blood pressure measurement should be performed. In some cases testing for adrenal and thyroid abnormalities should also be performed. In the syncopal patient, however, these tests are most usually normal; however, it is important to perform them to rule out some non-cardiogenic causes of collapse.

A resting electrocardiogram (ECG) should be obtained and the rhythm should be evaluated for at least 1 minute if not longer and while the animal is calm and it is excited. In dogs with bradycardia ECG should be evaluated a second time following the administration of atropine 0.04 mg/kg IV or SC. Dogs with underlying sinus node disease will show an inadequate response (heart rate increase to <140 bpm). Dogs with vagal tone as the underlying mechanism for bradycardia typically have heart rates that increase above 160 bpm. Normal heart rates on transient baseline ECGs, however, do not completely rule out arrhythmias as the underlying cause of the syncopal episode.

Thoracic radiographs should be performed to evaluate lungs, pleural space, mediastinum, and pulmonary vasculature as well as normal cardiac size and shape. Echocardiogram should be performed even if no murmurs are ausculted on physical examination to assess global cardiac function and to rule out the present of pericardial disease and obstructive cardiac masses.

In the face of finding all of the aforementioned test to be relatively normal (blood work, ECG, radiographs, and echocardiography) the clinician should consider ambulatory ECG monitoring with either Holter or event monitoring. Ambulatory monitoring can help identify or exclude cardiac arrhythmias as a cause for syncope in some animals.

Holter monitoring is 24 to 48 hours of continuous ECG monitoring. It is most likely to be diagnostic of syncopal events in animals with multiple and frequent syncopal episodes. To make a definitive diagnosis a syncopal episode must occur while the animal is being monitored. However, just because frequent events are occurring doesn't increase the likelihood of an event occurring during testing. Holter monitoring does allow one to identify any arrhythmia and quantitate the severity of arrhythmias that might increase the suspicion that the syncopal events are induced by arrhythmias. Because arrhythmias often occur without clinical signs this ability to evaluate the entire recording period is a very useful aspect of Holter monitoring. Holter monitors are also very useful for assessment of anti-arrhythmic therapy efficacy.

Event monitors are typically worn for 1 to 2 weeks periods in our patients that allow longer periods of assessment than with Holter monitoring. The event recording system does need to be activated when an event is observed. The monitor then saves to memory a portion of the recording prior to and after activation. The save recording is then transmitted via telephone to be printed. Event recorders have a higher diagnostic yield than Holter monitors; however, their biggest disadvantage is that they do not save recordings of potentially significant arrhythmias unless activated and they can not quantify the frequency of arrhythmias.

TREATMENT

Therapy of animals with syncope episodes is intended to manage the underlying disease and avoidance of precipitating activities such as excitement as much as one can. In as such treatment of specific causes is sometimes obvious for example correcting anemia or treating respiratory or metabolic disorders.

In the case of heart failure patients: addressing proper management of the patient in heart failure: Institute appropriate therapy with diuretics, angiotensin-converting enzyme inhibitors (ACE-I), and inotropic support if needed. In the case of patients who are already being treated with triple therapy, optimizing drug therapy dosages or stacking additional medications such as additional diuretics or vasodilators may help to place the patient in a more positive hemodynamic state and thus resolving syncopal signs.

If tachyarrhythmias are the apparent cause, treating with the appropriate anti-arrhythmic (or combination of anti-arrhythmic) will reduce or eliminate the number and severity of the arrhythmias such that the signs are eliminated. In the case of those arrhythmias that can not be eliminated such as atrial fibrillation associated with advanced heart disease, than using drug combinations that slows the number of impulses that cross the AV node to the ventricles will appropriately slow the heart rate enough to allow for appropriate ventricular filling and contraction that syncopal signs are eliminated or reduced significantly.

In the case of bradyarrhythmias, than pacemaker therapy may be warranted; especially those cases that don't respond to atropine trials. Other strategies that have been effective, at least anecdotally include using theophylline or aminophylline to attempt to increase heart rate. We have found that often this therapy may be effective early but becomes ineffective as time passes on. We have also successfully employed pacemaker therapy in animals where syncope was apparently induced by coughing and the cause of the cough could not be resolved (ie, severe LA enlargement).

In the rare cases of neurocardiogenic syncope, pacemaker therapy is not likely to alter the hypotension that results. In suspected cases, therapy with beta-blockers can be used to blunt the initiating sympathetically induced tachycardia and the hyperkinetic ventricular contractions that stimulate the mechanoreceptors. The concern with utilizing beta-blocker therapy along is exacerbation of the resultant bradycardia thus these patients should be monitored very closely and combination of drug and pacemaker therapy may be the most appropriate for these animals.

SUMMARY

Syncope can be a very difficult diagnosis and hard to distinguish from seizures or other causes of collapse. An adequate physical examination and understanding of the etiology and pathophysiology along with a stepwise approach to animals presenting with this clinical complaint can expedite uncovering the underlying cause and allow for early intervention for these animals.

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Table 1. Diseases Associated with Mechanism of Syncope

Cardiovascular	**Hypotensive/Reflexive**
A) Arrhythmias	**A) Neurologic**
1. Tachyarrhythmias	1. Brain Tumor
a) Ventricular Tachycardia	2. Thromboembolism
b) Supraventricular tachycardia	3. Seizures
c) Atrial fibrillation	**B) Metabolic/ Hematologic**
2. Bradyarrhythmias	1. Acute Hemorrhage
a) Sinus node disease	2. Anemia
b) Atrioventricular block (high grade)	a) Hemolysis
B) Impaired Forward Cardiac Output	3. Hypoxemia
1. Myocardial Failure	a) Primary respiratory disease
a) Dilated cardiomyopathy	b) Pleural space
2. Severe Valvular Regurgitation	4. Hypoglycemia
C) Impaired Filling	**C) Neurocardiogenic**
1. Hypertrophic cardiomyopathy	
2. Pericardial effusion	**D) Tussive (cough)**
3. Intracardiac tumor	
D) Outflow Obstruction	**E) Micturition, defecation**
1. Subaortic stenosis	
2. intracardiac tumor	
3. Pulmonic stenosis	
4. Pulmonary hypertension	
E) Cyanotic Heart Disease	
1. Tetralogy of Fallot	
2. Other right to left shunting defects	

DISEASES OF THE PERICARDIUM

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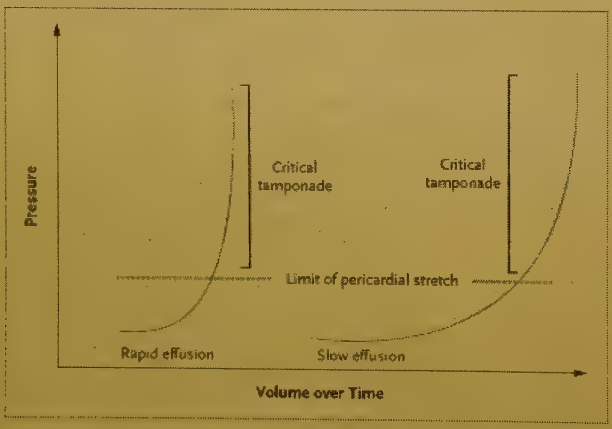
Pericardial diseases are commonly overlooked or mistaken for other cardiac and noncardiac disorders. This is most likely secondary to the fact that pericardial disease represents a relatively small portion of clinically important cardiovascular diseases in dogs and cats and because the physical findings may be relatively indistinct. Paramount to the understanding of clinical presentation, diagnosis and therapy of pericardial disease is the realization of the underlying pathophysiology.

Pericardial disease cause **diastolic cardiac dysfunction** with no to minimal if any alterations in intrinsic systolic function. Elevated intrapericardial pressure inhibits diastolic cardiac filling and as this pressure rises above cardiac diastolic filling pressure, **cardiac tamponade** occurs which can present clinically in either acute or chronic forms. In either case cardiac tamponade results in a significant reduction in preload for any given venous filling pressure. Reducing preload results in decreased cardiac output assuming heart rate, cardiac contractility and vascular resistance is unchanged.

The body's response to the aforementioned decreased cardiac output include increased sympathetic tone and activation of the renin-angiotensin-aldosterone system (RAAS) with resultant increased heart rate, augmented cardiac contractility, sodium and water retention and increased peripheral vascular resistance. The increase plasma volume increases the preload which in combination with the increased heart rate and improved contractility; initially restores cardiac output to near normal. The increased preload, however, is attained at the expense of the elevated venous filling pressures which is eventually manifest as signs of congestion. Because the right heart is more sensitive to pericardial pressure, the signs of right-sided congestive heart failure (jugular venous distention, hepatomegaly, ascites, +/- pleural effusion) predominate.



ETIOLOGY

Congenital

Several congenital diseases of the pericardium are recognized in small animal species. Peritoneopericardial diaphragmatic hernias (PPDH) are the most common type of abnormality encountered. Intrapericardial cysts and partial pericardial defects have been sporadically reported which congenital complete absence of the pericardium is exceedingly rare.

Congenital PPDH occurs as an isolated defect and in association with umbilical hernias, malformed or absent sternebrae, pectus excavatum, and a variety of congenital heart defects. Clinical signs in dogs and cats with PPDH vary in relation to the organs that are displaced into the pericardium and the degree to which the blood supply and function of these organs are compromised. The liver is herniated most frequently, followed by the small intestine, spleen, and stomach. Thus, signs of gastrointestinal disease-vomiting, anorexia, and diarrhea are common in dogs and cats with PPDH. Respiratory abnormalities, varying from coughing or wheezing to severe dyspnea, are the next most frequently observed clinical signs. Only rarely are signs of heart failure and cardiac tamponade observed.

Acquired

Pericardial effusion is the most common cause of pericardial disease in the dog (not so common in cats) and accounts for more than 90% of pericardial disorders, whereas constrictive pericarditis is uncommon by comparison. Clinically significant effusions are most commonly secondary to neoplasia representing 60% to 70% of occurrences with **hemangiosarcomas** or **heart base tumors (chemodectomas or thyroid carcinomas)** occurring most commonly. Neoplastic effusions usually occur in dogs greater than 7 years of age (average 9+ years). German shepherd dogs and Golden retrievers are predisposed to hemangiosarcoma. Brachycephalic breeds (Boxers, Boston terriers) are reportedly predisposed to heart base tumors. Mesothelioma is the most common primary tumor of the pericardium. Idiopathic pericardial effusions comprise about 30% of clinical cases. Most commonly affected are medium to large breed, middle-aged (average age 7 years) male dogs. The German shepherd dog also is over-represented in this disorder. In cats, pericardial effusion is often associated with feline cardiomyopathy, feline infectious peritonitis, and neoplasia (primarily lymphosarcoma).

DIAGNOSIS

Physical Examination

Clinically most animals with pericardial effusion present with a vague history of lethargy, weakness, exercise intolerance, and anorexia. More severely compromised animals will have obvious clinical signs of abdominal distension, respiratory difficulty, or syncope. Rapidly developing effusions such as seen with **atrial tear, traumatic laceration, bleeding neoplasm** cause acute hypotension, weakness, dyspnea, collapse, and, on occasion, sudden death.

On physical exam, heart sounds are usually muffled, and in cases with pleural effusion lung sounds may be diminished as well. Hepatomegaly and free abdominal fluid are common findings unless the effusion is of very sudden onset. Femoral arterial pulses are often weak as a consequence of peripheral vasoconstriction and reduced stroke volume. **Pulsus paradoxus** (inspiratory fall in systemic arterial pressure exceeding 10 mmHg) is a valuable clinical sign that may be seen in cardiac tamponade. When the systemic veins are distended and ventricular filling is limited by cardiac tamponade, inspiration increases venous return to the right side of the heart and further raises intrapericardial pressure, reducing left ventricular dispensibility. The interventricular septum is displaced toward the left ventricle, causing a significant reduction in left ventricular filling, stroke volume, and systemic blood pressure.

Jugular venous distention or a positive hepatojugular reflux is almost invariably present. Measurement of central venous pressure (CVP) is valuable when evaluation of the jugular veins is equivocal. Measures of CVP usually exceed 10-12 mmHg (normal = < 6 mmHg) when cardiac tamponade is present.

Radiography

Thoracic radiography typically demonstrates a markedly enlarged, globoid cardiac silhouette. It some cases evidence of pulmonary underperfusion may be noted where there is significant reductions in cardiac output. Pleural effusion may or may not be present. In cases of peritoneal pericardial diaphragmatic hernia, variable radiographic densities within the cardiac silhouette and sternal abnormalities may be noted.

Electrocardiography

Electrocardiographic abnormalities classically seen with pericardial effusion include low amplitude complex size, electrical alternans (alternating variation in the amplitude of QRS complexes with every other beat), and ST segment elevation or depression. Dampening of the PQRS complexes by the accumulated fluid and diminished cardiac filling are responsible for observed low amplitude complexes. Electrical alternans is caused by the rhythmic swinging of the heart within the fluid filled pericardial sac. Atrial arrhythmias, including atrial fibrillation, are also observed on occasion. Please note the absence of any or all of these findings in no way rules out a diagnosis of pericardial effusion.

Echocardiography

Echocardiography is the most sensitive and specific noninvasive method of detecting pericardial effusion. Echocardiography can detect as little as 15 mL of intrapericardial fluid. An anechoic space between the epicardium and pericardium is the classic echocardiographic finding in pericardial effusion. The heart can often be observed swinging from side to side within the pericardium (demonstrates the cause of electrical alternans). Overall cardiac chamber size is diminished when pericardial effusion causes impaired cardiac filling. The right ventricular free wall (RVFW) often appears hyperechoic due to the dramatic difference in echogenicity between the pericardial effusion and myocardium. This should not be interpreted as an abnormality of the RVFW. Echocardiography often permits visualization of intrapericardiac or cardiac mass lesions. Whenever possible, echocardiography should be performed before pericardiocentesis, as the pericardial fluid will greatly enhance the ability to visualize mass lesions on the heart or pericardium. It is important to realize that small tumors can be easily missed.

THERAPY

Pericardiocentesis

Pericardiocentesis is the treatment of choice for stabilization of dogs and cats with pericardial effusion and cardiac tamponade and is associated with minimal complications. A right-sided approach lessens the chance of coronary artery damage. Surgical preparation of a large area over the right hemithorax is necessary prior to performing pericardiocentesis. Local anesthesia is usually adequate however mild sedation is sometimes necessary.

Thoracic radiographs can be helpful in determining the optimal puncture site however most times this can be performed between the fourth to sixth rib spaces at the costocondral junction. The size of the needle or catheter used is dependent on the size of the animal. In cats a 19- or 21-gauge butterfly catheter may be adequate while in large dogs a 16-gauge over-the-needle catheter may be needed. The needle or catheter should be attached to a three-way stopcock, extension tubing, and a syringe, to allow constant negative pressure to be applied during insertion and drainage. Care should be taken to avoid the large vessels that run along the caudal border of the ribs. Once the catheter has been inserted through the skin, negative pressure should be applied. While monitoring the ECG, the catheter is advanced toward the heart. If pleural effusion is present, it will be obtained immediately upon entering the thoracic cavity. It is most commonly a clear to pale yellow color. As the catheter is advanced and contacts the pericardium, a scratching sensation will be noticed. Minimal advancement will result in penetration of the pericardium. Most pericardial effusions are hemorrhagic and have a "port wine" appearance. Once effusion of this character is obtained, the catheter should be advanced over the needle, and the needle removed. The remainder of the fluid should then be drained using the catheter. Advancing the needle too far will result in contact with the epicardium. This is often felt as a tapping or more intense scratching sensation and commonly results in ventricular arrhythmias. These arrhythmias are usually self-limiting following retraction of the needle or catheter.

Aspirated fluid should be compared with peripheral blood (PCV, protein, xanthochromia, clotting) and the pericardial sac subsequently drained. Pericardial effusion can be differentiated from peripheral blood in that it rarely clots unless it is from very recent hemorrhage. Routine cytology and fluid analysis are prudently obtained to exclude bacterial, fungal, or obvious neoplastic etiologies. Culture and sensitivity is performed only is cytology indicates a need for this test. It is usually **not** possible to distinguish the most common neoplastic effusates (hemangiosarcoma, heart base tumors) from idiopathic effusions on the basis of red cell or white cell counts, protein content, or by cytologic examination. Nor is the pH of the fluid a reliable indicator of the etiology of the effusion.

With idiopathic hemorrhagic pericardial effusion, pericardiocentesis is curative in approximately 50% of the cases. In the remainder, repeat centesis is necessary to control clinical signs. Fluid may reaccumulate rapidly or may not recur for years. In those requiring more than two centeses, we recommend performing subtotal pericardiectomy or periocardiotomy. With aortic body tumors subtotal pericardiectomy or pericardiotomy may afford palliation for up three years as these tumors are slow to grow and metastasize. Hemangiosarcoma of the right atrium is associated with a poor long-term prognosis. Most mass lesions involving the right atrium or right ventricle are not amenable to surgical removal. Those involving the right auricular appendage may be removed by auriculectomy; however, is still associated with poor prognosis.

Newer techniques such as thorascopic pericardiectomy and percutaneous pericardial balloon dilation may be reasonable alternatives to subtotal pericardiectomy in both neoplastic and benign effusions. This may provide significant palliation for patients with pericardial effusion and the resultant cardiac tamponade without necessitating a thoracotomy. These techniques allow the pericardial fluid to drain into the pleural space to be reabsorbed. Thorascopic procedures may have the advantage of being able to obtain samples of pericardium for histopathology over ballooning techniques however the procedure remains more costly than ballooning procedures.

Prognosis

The prognosis is good for patients with idiopathic effusions or effusions due to pericardial cysts or peritoneopericardial hernias. The prognosis for dogs with hemangiosarcoma is poor even with aggressive surgical and medical therapy. The prospects for animals with heart base tumors are more variable. Many dogs with slow growing chemodectomas experience long survival times with good quality of life for a year or more following subtotal pericardiectomy.

References are available from the author upon request.

DIAGNOSIS AND MANAGEMENT OF SYNCOPE

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Syncope is the loss of consciousness due to inadequate perfusion to the brain. Although some points from the description of a 'collapse' can differentiate true syncope from a seizure, it is not always possible to do so. Always the many causes of syncope and seizures should be consider in the early phase of making the diagnosis. The cardiovascular causes of syncope can be categorized into those which are (1) due to cardiac arrhythmias (severe tachycardias or profound bradycardia), (2) obstruction to output (subaortic stenosis, tumor obstruction, (3) poor systolic function (dilated cardiomyopathy), (4) restriction to cardiac filling (cardiac tamponade), (5) systemic hypotension or (5) severe hypoxia (right to left shunt such as tetralogy of Fallot).

What are the diagnostics that are done in the evaluation of weakness and collapse? Radiography will reveal evidence of pulmonary pathology and usually give an appreciation of cardiac size. Electrocardiography may provide the evidence for the diagnosis of the rhythm disorder, although 24-hour ambulatory (Holter) monitoring, event recorders, or implantable recording devices may be required. Echocardiography will give the structure and functional characteristics to determine the specific disease. Finally, blood pressure and laboratory tests will clear the animal of other diseases and provide the foundation to know that drug therapy is not contraindicated if underlying organ dysfunction is severe.

What are the rhythm abnormalities that can result in weakness or collapse? When the heart rate is too slow or too fast, weakness can occur. The degree of these extremes dictates the severity of the clinical signs. The parameters include both the rate and the duration of the extreme in rate. Critical to this factor is the generation of the systemic blood pressure. For example a heart rate of greater than 260 bpm is more devastating than a rate of 200 bpm, but if the faster rate persist for only a few seconds and the latter for hours the bad consequences are greater. This same thought follows through with the length and rate of bradycardias. When the extreme rates cause a loss of cerebral blood flow (inadequate pressure) for more than 8 seconds, then collapse or syncope will result. The most common tachycardias that can cause weakness include atrial fibrillation, atrial tachycardia, and ventricular tachycardia. The most common bradycardias include third-degree heart block, advanced second-degree heart block, and sick sinus syndrome. It is also possible for syncope to be neurogenically mediated (eg, associated with postural changes, coughing, urination) whereby a mismatch of heart rate and blood pressure result in inadequate cerebral perfusion.

TREATING ATRIAL FIBRILLATION

The following drugs are ones that can be used to control heart rate by slowing AV nodal conduction.

1. **Digoxin alone**. 0.003 to 0.005 mg/kg BID, lean body weight, frequently reduce this calculated dose by 25% for extra safety, titrate to safe serum level of approximately 0.7 to 1.0 ng/mL. This is lower than past recommendations. *or*
2. **Diltiazem (extended release) alone.** 2 to 4 mg/kg twice daily. Some dogs require higher doses, particularly Great Danes (usual Great Dane requires 240 mg BID), In dogs with very poor systolic function use the lower end of dose range to start; however, a surprising number tolerate and need the highest dose.
3. **Combination of digoxin and diltiazem** dose of either or both may be reduced when used in combination. This combination is most successful when heart failure exists because more sympathetic influence pushes the ventricular response rate higher, thus, the combination is most effective than any drug alone. Watch for excessive slowing of ventricular rate or excessively long pauses (eg, > 3 sec).

In a dog with acute heart failure due to dilated cardiomyopathy and marked tachycardia due to atrial fibrillation the goals must be prioritized. Most of the time severe dyspnea is present in addition to the tachycardia of the atrial fibrillation. The dog must breath before all else. Aggressive, short-term treatment with diuretics is given with acute treatment with nitroglycerin, and some may use nitroprusside with continuous monitoring. The dilemma is whether to treat the dog with dobutamine (improve output) or diltiazem (control heart rate response). A second dilemma concerns the route of drug administration. In the dog that is in complete distress the intravenous route is obvious, but not all dogs are in this most dire position. Some could be treated orally. Response to oral diltiazem can be rapid; however, if there is a negative response the effects can be more protracted if the long-acting preparations are used such as Dilacor®. The effects of regular diltiazem do not last long in the dog and require frequent administration; however, this can be an advantage in a dog where the IV route is not selected, but the long acting medication is not desirable as yet. The unfortunate problem is that with calcium channel blockers and beta-adrenergic blockers the heart rate control comes with the price of hypotension in many dogs with myocardial failure. This is why a combination of treatment with digoxin can be advantageous, but the dog must live long enough to have all the medications achieve adequate blood levels. Once this is achieved, titrating to the oral doses can begin.

TREATING VENTRICULAR TACHYCARDIA

One of the common ventricular tachycardic rhythms that causes syncope occurs in the boxer with arrhythmogenic right ventricular cardiomyopathy. The ventricular tachycardia can be as rapid as 300 bpm resulting in severe hypotension. A plan that can be used to treat such dogs is shown in Table 1.

TREATING BRADYCARDIAS THAT ARE PERMANENT (NOT DRUG-INDUCED)

In dogs with bradycardias as the cause of the syncope, pacemaker implantation is the ideal therapy. This is now a common procedure in the dog and is for the most part successful.

TREATING OBSTRUCTION TO OUTPUT

Some dogs with subaortic stenosis and obstruction to output particularly during exercise may benefit from titration of beta-adrenergic blockade. Only through a clinical trial of such treatment can it be determined in a specific dog that they will in fact improve. On occasion a dog treated with a beta-adrenergic blocker and subaortic stenosis collapses more often and the treatment is discontinued. Some dogs that have heart base tumors (chemodectomas) will collapse; however, it is not known if this collapse is due to obstruction or to some type of neuromediated imbalance from the neoplasia.

RESTRICTION TO FILLING DUE TO CARDIAC TAMPONADE

Pericardiocentesis is required as an emergency procedure. The next major issue to resolve is cause: neoplasia or not. Most of the time echocardiography provides this answer. The most common neoplasias include hemangiosarcoma, chemodectoma, thyroid carcinoma, and lymphosarcoma. Some dogs with pericardial effusion have idiopathic pericarditis and can be treated with pericardectomy.

Table 1. Management of Syncope

Timing of Exam After Diagnosis	Tests	Purpose of Tests	Interpretation of Tests
Initial	Physical examination, blood chemistry, ECG, thoracic radiographs, echocardiography, Holter monitoring	Vital to establish baseline arrhythmia frequency. To determine myocardial function and cardiac size	Judgment of drug efficacy cannot be determined without baseline data. Holter monitoring is required for accuracy
1 to 2 weeks	Recheck Holter after beginning drug. Treatment is most often sotalol at 2 to 3 mg/kg twice daily	To evaluate if an adequate reduction in arrhythmias has occurred and to assess for other ECG drug effects	If inadequate response then the dose is increased. Most average to large boxers require 80 mg twice daily
3 to 4 weeks	Recheck Holter if drug dose was changed at week 1 or 2	To see if dose change decreased the arrhythmia counts	Establish longer-term dose
3 months (optional)	Recheck Holter	To assure antiarrhythmic effect	Change dose if needed and assess dog's response to therapy
6 months	Recheck Holter and echocardiogram	To assure antiarrhythmic effect and to determine if myocardial function remains stable	Add medication is myocardial function is decreasing
12 months	Recheck Holter and echocardiogram	To assure antiarrhythmic effect and to determine if myocardial function remains stable	If antiarrhythmic effect holds and myocardial function is normal then check Holter every 6 months. An abbreviated echocardiogram can be done to track function

FELINE THROMBOEMBOLISM

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In this review of thromboembolism in the cat, the short- and long-term therapeutic management will be discussed. Although the focus herein is on treatment of thromboembolization, it is imperative that the following major points be remembered: (1) Almost all cats with thromboembolism have important underlying cardiac disease; (2) Approximately half of the cats with thromboembolism have concurrent clinical signs of congestive heart failure and these need to be considered in the prognosis and treatment; (3) Treatment of thromboembolism in the acute phase can be very challenging if reperfusion injury occurs with survival in part dependent on meticulous monitoring and careful treatment; (4) Long-term treatment to decrease the reoccurrence of thromboembolism is controversial as to the drug choice and dose; and (5) Despite the challenges of thromboembolism (eg, likelihood of severe heart disease, difficulties in treating the acute consequences, expense of treatment, and unknowns regarding the correct long-term treatment for both the cardiac and thromboembolic disease), enough cats survive for an 'adequate' amount of time that the rendered care is deemed worthy by many owners even when they understand the problems.

THE CAUSE OF THE CLINICAL PRESENTATION

Thromboembolism occurs most commonly as the result of cardiac disease in the cat with a clot lodged in the distal aorta and iliac arteries. The arterial occlusion alone is not the cause of the reduced circulation, but the effects of the thrombus cause a cascade of vasoconstriction events that reduce collateral circulation. In order to reproduce the clinical disease experimentally, arterial ligation with the injection of bovine thrombin is required. Thus, it is not primary channel blockade that causes the ischemic neuromyopathy. The cat has many collateral vessels to call upon from the vertebral arterial system, but when this fails to happen the clinical syndrome ensues. Additionally, it is the reopening of these collateral vessels in the 12 to 24 hours after the thromboembolic event that result in the reperfusion injury that kills many cats.

CLINICAL SIGNS OF THROMBOEMBOLISM

Thromboembolism may be the first clinical sign of cardiomyopathy in many cats. Clinical signs include both the direct consequences of thromboembolism and the associated cardiac disease: acute rear limb paralysis, pain, depression, or dyspnea. The majority of cats have both rear limbs affected, although a single limb (rear or front) can be embolized. Occasionally, a cat may have paresis, rather than paralysis (paraplegia) if affected to a lesser degree. The physical examination of cats with aortic thromboembolism might include (1) the absence of femoral pulses, (2) firm to hard cranial tibial and gastrocnemius muscles, (3) pale to black cold foot pads, (4) absence of deep pain response, (5) absence of limb motion below the upper thigh, (6) hypothermia, (7) lack of anal tone and distended bladder, (8) abdominal pain if the mesenteric artery also has been embolized, (9) tachypnea and tachycardia (seen with cardiovascular compromise, stress and pain), (10) bradycardia or irregular cardiac rhythm, (11) heart murmur or gallop sound, or (12) varying degrees of depression.

As with most diseases, the severity of the disease and the resulting clinical presentation are variable. Clinical signs that indicate a 'better' prognosis include pad color that is pale pink, tail movement, good anal tone, upper thigh muscle control, normal mental acuity, eupneic, and normal body temperature. Also, cats have a better prognosis if they have hypertrophic cardiomyopathy and not restrictive cardiomyopathy. In addition, left atrial size affects prognosis with severe dilation being more ominous indicator. The prognosis is worse if congestive heart failure is present.

THE DIAGNOSTIC PLAN

The diagnostic evaluation of the cat with thromboembolism includes blood pressure, echocardiography, thoracic radiography, serum chemistry, and electrocardiography. Although the blood pressure determination in the hind limbs will not be accurate, an assessment from the forelimbs is important to gauge the overall status of the cat. Echocardiography will reveal the type of cardiomyopathy, the severity of the hypertrophy and/or fibrosis, systolic and diastolic dysfunction, size of the atria, presence of pleural effusion, and presence intra-atrial blood stasis or clots. Thoracic radiography permits the determination of pulmonary edema or pleural effusion. Pulmonary edema can exist even if not suspected from the auscultation of the lungs. Moreover, tachypnea is seen in the majority of these cats. The cause can be either pulmonary edema, pain, or both. The radiograph helps to determine if treatment for fluid retention is required.

SERUM CHEMISTRY ABNORMALITIES ARE COMMON AND EXTENSIVE

Azotemia, hyperglycemia, elevation in muscle enzymes (creatine phosphokinase, aspartate aminotransferase and alanine aminotransferase), hyperkalemia, acidosis, hyperphosphatemia, and hypocalcemia can be documented. Azotemia is usually due to poor perfusion to the kidneys and it is this same mechanism that explains the hyperphosphotemia. Hyperglycemia is hypothesized to be due to two factors: stress and increased lactate. Stress causes an increase in adrenergic hormones that inhibits insulin secretion and this in turn causes the increase in blood glucose. Also contributing to the stress response are high glucagon and cortisol levels. Concomitant with this is that lactate levels are high due to muscle anaerobic glycolysis. Lactate is a major gluconeogenic precursor to cause hyperglycemia. It is believed that insulin resistance is likely not responsible for the hyperglycemia in cats. Elevation in muscle enzymes particularly that of creatine phosphokinase, can be dramatic in cats with thromboembolism due to the muscle necrosis. Poor renal perfusion accounts for the hyperphosphatemia, but again the death of muscle serves as a source for massive quantities of phosphorus. The excessive phosphorus binds to calcium and this accounts for the hypocalcemia. Metabolic acidosis develops in response to the lactic acidosis reaching levels that demand specific treatment. All of these biochemical alterations change over time after the thromboembolic event. The ideal situation is for them to return to normal; however, it is important to particularly watch the potassium concentration as it can increase as reperfusion develops.

Electrocardiography is vital on admission not only for the evaluation of the rhythm, but to ascertain the electrocardiographic evidence of the potassium concentration. Frequently, the ECG on admission is normal, but once reperfusion begins (as early as 6 hours after thromboembolism) the potassium concentrations can elevate quickly. Monitoring of the ECG provides a means to monitor the serum potassium level. Attention should be paid to the P wave, S wave and T wave. Most frequently cats will develop S waves, the P wave flattens and the T wave flips to positive as an indicator that the potassium is increasing. It is vital that the serum potassium be rechecked so that treatment can be started early enough to be of benefit. Severe abnormalities in conduction and rhythm progress as the potassium levels increase.

OVERVIEW OF TREATMENT

Treatment of thromboembolism is a matter of multitasking, changing problems, and shifting goals. It is important to realize that the specific treatment is dictated by the amount of time that elapses after thromboembolism. The discussion of treatment will be divided into four stages:

1. Immediate treatment (0 to 6 hours post-thromboembolism);
2. Reperfusion treatment (6 to 18 hours post-thromboembolism);
3. Early recovery from thromboembolism (18 hours to 7 days post-thromboembolism);
4. Long-term management (home care).

IMMEDIATE TREATMENT

The initial problems that coexist with thromboembolism are referable to cardiomyopathy and include (1) respiratory distress because of pulmonary edema and (2) cardiovascular shock. Pain and anxiety occur because of the thromboembolism. Tachypnea and dyspnea are frequently present and the reason for these signs may not be clear without thoracic radiography to determine the presence or not of coexisting pulmonary edema. In the ideal situation the thrombus would be removed within 4 hours, but this is not likely to happen because the availability of the procedure is uncommon and it is unknown if cats can survive such surgery. Also, it would be ideal if the clot could be treated immediately with a clot 'buster' [eg, tissue plasminogen activating factor (TPA)] early such that the amount of cell death is decreased to diminish the problems of reperfusion injury. Again, the proper method, drug, and talent to offer this treatment is currently lacking in veterinary medicine.

IMMEDIATE ANTICOAGULANT TREATMENT

For years, the use of heparin in acute thromboembosis has been purported in the acute situation. We need to all consider the evidence for this treatment and its value. We actually do not have any evidence of its effectiveness in improving the state of these cats. Heparin (unfractionated heparin) is a heterogeneous combination of heparin molecules with disaccharide units of varying lengths. The length of the molecule affects the action. The different size heparin molecules bind in different ways and affect the coagulation in varying degrees. Also, unfractionated heparin has a high affinity to binding with serum protein and cells. Once these are loaded the heparin binds to thrombin (Factor IIa) and form a thrombin-antithrombin-complex that is irreversible. Unfractionated heparin inhibits both Factor Xa and Factor IIa. Inhibition of Factor IIa requires the long sugar residues found in unfractionated heparin and these are not found in the low molecular weight heparins (LMWH). After treatment with heparin, it is possible because of the purported decrease in antithrombin III, that there is a hypercoagulable period, but we do not know if such a time actually exists in cats. The unfractionated heparin dose in the cat is 100 IU/kg given subcutaneously and repeated at 6 hour intervals after a loading dose of. The efficacy has not been evaluated.

Recently LMWH have been professed as better than unfractionated heparin. These heparins are more uniform in their size with fragments of 4 to 8 kD with an average chain length of 15 subunits and 80% < 40 subunits, this is in contrast to the heterogenous mixture of 10 to 100 subunits for the unfractionated heparin. The LMWH are short and bind primarily to Factor Xa and not to Factor IIa. It is may be that this type of inhibition is adequate for preventing clot formation. The LMWH do not require the loading dose that unfractionated heparin requires. Monitoring of LMWH effect is done by measuring Factor Xa activity. Two LMWHs are enoxaparin (Lovenox) and dalteparin (Fragmin). These formulations are approximately 4 times as expensive as unfractionated heparin. The dose of enoxaparin has been 1 to 1.5 mg/kg subcutaneously. The dose of dalteparin used in cats has been approximately 100 IU/kg given subcutaneously every 12 hours has been given to cats. Early studies suggest the half-life of LMWH is short in the cat and that dosing must be more frequent. Although this is not problematic for the hospitalized cat, it is a dilemma if treatment is to be administered at home. Few owners would be able to inject a cat three times per day. The validity of these drugs and the proper dosage in the acute situation of thromboembolism in the cat have not been studied.

IMMEDIATE CONTROL OF CONGESTIVE HEART FAILURE

When pulmonary edema is present diuresis is required with parental administration of furosemide. The dose is important and must be adjusted to the patient and the response. Usually a dose of 1 mg/kg given intravenously is given when the cat has pulmonary edema, but is not in a critical situation when more aggressive treatment is used. The response is assessed and additional doses given as needed. In some cats it may be important to also treat with nitroglycerin ointment with blood pressure monitoring. This treatment is in conjunction with the assessment of hyperkalemia, renal perfusion and importantly cardiovascular shock. Each of these three problems demand fluid therapy, but for a cat with a compromised cardiac status and pulmonary edema, fluids can be catastrophic. However, it is the truth that in such cases the cat may be receiving fluids at half-maintenance level while also getting furosemide. Constant monitoring of mental acuity, blood pressure, heart rate and respiratory rate assist in making the needed adjustments in this 'contradictory regimen of therapy'. The dose of furosemide in cats with critical pulmonary edema and thromboembolism may require repeating every 2 to 4 hours until a response of improvement are seen. When cardiogenic shock is present intravenous infusion with dobutamine may be required in this difficult situation.

It is in the first few hours that control of pain and anxiety are considered somewhat important. Pain and anxiety increase the sympathetic tone and this is very detrimental to cats with cardiomyopathy. Consequently, treatment with medication that would relieve these symptoms is ideal so long as the price is not excessive sedation and hypotension. In the past, acepromazine has been recommended for such treatment; however, this drug is not recommended. Today butorphanol at 0.2 to 0.4 mg/kg subcutaneously every 4 hours or hydromorphone at 0.05 to 0.1 mg/kg subcutaneously are most frequently used. Butorphanol will not give as much analgesia as the hydromorphone, but the latter is more likely to cause dysphoria. Over-sedation can compromise the ability to judge the status of cardiovascular shock and mentation. Other medications such as fentanyl patches are not recommended because they take too long be effective. This is an important consideration because pain in cats with thromboembolism last a relatively short time of less than 6 to 10 hours.

REPERFUSION INJURY

Cats will suffer from reperfusion injury to varying degrees depending on the vascular hyperpermeability, hyperkalemia, edema and acidosis present. In some, there will be no apparent consequences while in others this is the cause of death. The problems to battle in this stage of treatment are hyperkalemia, acidosis, azotemia, cardiac rhythm and conduction problems, shock, and compromised cardiac function. Pulmonary edema must continue to be treated as demanded in cats that suffer from this in addition to the thromboembolism. The clinical signs of reperfusion include depression, arrhythmias, conduction disturbances, and in general, 'crashing.' ECG monitoring permits notification of changes in serum potassium levels. Additionally, monitoring of the serum potassium levels every 2 to 4 hours may be required when possible. Knowing when the potassium concentration is increasing and acting on this situation early is key to success. Acidosis will develop in these cats and contribute to the hyperkalemia. The aggressiveness in the treatment of hyperkalemia depends on its severity. Treatment can include modest fluid therapy with NaCl (careful to watch for pulmonary edema), intravenous glucose (but if the cat is already hyperglycemic this is not effective), sodium bicarbonate (effective for the acidosis too), very low doses of insulin (give with glucose and monitor), to intravenous calcium (directly counteracts the cellular effects of hyperkalemia). Always during the selected treatment the potassium concentration is monitored for effectiveness of treatment and to be alerted to the time to stop treatment. This is important because overshooting treatment past the reperfusion period will result in hypokalemia. Frequently, specific treatment for the heart disease such as ACE inhibitors is not given at this point in the treatment of these cats. Azotemia can be mild to severe depending on the cardiac status, underlying renal reserve, renal perfusion, presence of renal emboli, severity of reperfusion, doses of furosemide required to control pulmonary edema, and fluid administration tolerated to assist during reperfusion. Monitoring blood pressure, heart rate, respiratory rate, mentation, and renal perfusion continue to be important. Pain relief at this stage of the disorder usually is not required.

EARLY RECOVERY FROM THROMBOEMBOLISM

Near the end of the reperfusion period the limbs can swell, sometimes dramatically. The skin can become erythematous and pitting edema can develop. Cats can loose the hair over the limbs. If a cat survives the reperfusion injury it is critical that the entire cat be reevaluated because the furosemide dose, quantity of fluids, specific treatment for hyperkalemia, and pain treatment all will need to be adjusted or eliminated. This is also the time that the monitoring of the physical state of the cat must not stop. Immediately after the intensity of treating a cat with severe reperfusion injury, a false sense of victory can occur and deterioration of the cat can be missed unless vigilance continues. This is especially true for decompensation of the heart and the acute development of pulmonary edema. During this time additional medications that are given orally for the heart can be started and these include ACE inhibitors, aspirin, and potentially clopidogrel. If the cat begins to eat at this time, this is a good prognostic indicator.

LONG-TERM MANAGEMENT

The problems to address in the long-term include treating the (1) underlying cardiac disease and managing congestive heart failure if present, (2) preventing reembolization, and (3) providing the needed care and management for recovery of the limbs form the thromboembolic event.

There remains controversy as to the correct treatment of cats with hypertrophic and restrictive cardiomyopathy. In general, cats that have had an episode of pulmonary edema are treated with angiotensin-converting enzyme (ACE) inhibitors, furosemide at a dose that prevents pulmonary edema and yet preserves renal perfusion. In cats that have not had an episode of pulmonary edema the use of beta-adrenegic blockers or calcium channel blockers is unclear. Given that the majority of cats that leave the hospital after thromboembolism die of congestive heart failure determination of the best treatment of the underlying heart disease is a paramount goal.

It is clear that these cats need treatment to prevent re-embolization which occurs at the rate of about 25% as reported in the most recent reports, but what is uncertain is how this is accomplished. For many decades some have suggested the use of aspirin, while others say it does no good. Studies in the early 1970s showed that experimentally cats treated with aspirin, if thromboembolism did occur, had less severe clinical signs and recovered quicker. But still, thromboembolism occurs. In humans aspirin alone is frequently inadequate to control thromboembolism, whereas, anticoagulation treatment decreases the recurrence. However, treatment with anticoagulants such as coumadin requires rigorous monitoring that is rarely possible in cats. The LMWH could be an alternative, although when these have been used thromboembolism still developed and the target levels were never obtained at the dose used and the half-life appears short. The latter is problematic because the drug must be administered parenterally and it appears that twice daily administration is inadequate. This type of treatment is likely not practical. Recently, an alternative treatment has been suggested which is antiplatelet rather than anticoagulation. This involves the combination of aspirin with another drug that works by a different mechanism to inhibit platelet aggregation. This drug is clopidogrel (Plavex) and recent studies have shown this to be a safe drug in cats.

The mediators of platelet activation include thrombin, ADP, collagen, and thromboxane A_2. Thrombin stimulates platelets to release ADP and thromboxane A_2. Collagen activates platelets to recruit other platelets. The antithrombotic effect of aspirin occurs by irreversibly acetylating cyclo-oxygenase to block formation of thromboxane, but it has no effect on platelet activation by thrombin and ADP. Clopidogrel which is a thienopyridine ADP receptor antagonist exerts its effect of inhibiting platelet aggregation through irreversible inhibition of ADP receptors on the platelet membrane blocks and indirectly reduces binding of fibrinogen and von Willebrand factor. It is the active metabolite (produced through hepatic metabolism) that is the active form of the drug. Clopidogrel also inhibits glycoprotein IIb/IIIa receptor complex and reduces serotonin release from platelets.

Only time will tell which cats will regenerate enough nerve with adequate muscle mass to restore ambulatory function. The amazing fact is, many cats can do this. Disappointingly, before the time has elapsed for these regenerative processes some cats may actually survive the ischemia and reperfusion only to have a leg that never recovers adequate perfusion for regeneration. Such a situation results in euthanasia or amputation of the limb. Some cats may require perfusion studies to determine the status that guides treatment. During the recovery of the limbs the act of dragging the limbs and the sensation return can cause problems. Necrosis, infection and self-mutilation can occur and undermine the success of saving the cat from the critical insult. Bandaging to protect the lower leg from abrasion when the cat drags its legs must be done with care because of the reduced circulation. If skin erosions develop aggressive treatment with cleansing, silver sulfadiazene ointment, and bandaging protection are required. The most common infection of such sores is *Pseudomonas aeruginosa*, similar to burn injuries. Immediate attention is required if a fever develops and an elevation in the white blood cell count. When this type of lesion develops the limb may not be salvaged and amputation is required. Although this is a desperate measure, it is surprising how cats can survive the surgery and live with the single hindlimb.

In summary, the treatment of thromboembolism in the cat entails multitasking and attention to detail. An understanding of the pathophysiology will guide us in designing studies to answer the clinical questions. We have made progress in the treatment of this disease, but there is still a long way to go. The fortunate situation is that there are cats that can survive despite our limited knowledge.

HOW TO TREAT ARRHYTHMIAS IN THE FACE OF HEART FAILURE

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MANAGEMENT OF ATRIAL FIBRILLATION WITH HEART FAILURE (NON-EMERGENCY)

Atrial fibrillation in dogs with heart failure is most common in large breed dogs [Dobermans with dilated cardiomyopathy (DCM), Boxers with arrhythmogenic right ventricular cardiomyopathy (ARVC)], giant breed dogs (Great Danes and Newfoundlands with DCM), dogs with degenerative valve disease (usually small dogs), occasional dog with severe left to right shunting and a patent ductus arteriosus. The most common clinical signs include dyspnea, coughing, weakness, weight loss, anorexia, exercise intolerance, and syncope. Ideally a complete physical examination, chemistry panel, blood pressure, thoracic radiograph, echocardiogram, electrocardiogram, and baseline 24-hour Holter monitoring are performed. The 24-hour Holter should be evaluated for the following:

1. Average heart rate, maximum and minimum heart rate
2. Length of time with rate greater than 120 b/m, length of time with rate less than 50 b/m
3. Number and length of pauses
4. Presence of any ventricular arrhythmias
5. Time of day or sleep/wake heart rate trend

TREATMENT CHOICES

The following drugs are ones that can be used to control heart rate by slowing AV nodal conduction.

- **Digoxin alone.** 0.003 to 0.005 mg/kg BID, lean body weight, frequently reduce this calculated dose by 25% for extra safety, titrate to safe serum level less than 1.5 ng/mL, aim for 0.7 to 1.0 ng/mL. This is lower than past recommendations. *or*
- **Diltiazem (extended release) alone.** 2 to 4 mg/kg twice daily. Some dogs require higher doses, particularly Great Danes (usual Great Dane requires 240 mg BID), In the dogs with very poor systolic function use the lower end of dose range to start; however, a surprising number tolerate and need the highest dose.
- **Combination of digoxin and diltiazem.** The dose of either or both may be reduced when used in combination. This combination is most successful when heart failure exists because more sympathetic influence pushes the ventricular response rate higher, thus, the combination is most effective than any drug alone. Watch for excessive slowing of ventricular rate or excessively long pauses (eg, > 3 sec).

The following are drugs used in the treatment of congestive failure (*indicates most commonly used treatment, **indicates frequently added to *commonly used treatment, ***indicates under investigation to add to * commonly used treatment):

- Modest sodium restriction, high protein diet (eggs), B vitamins, antioxidants
- *Furosemide 1 to 4 mg/kg once to three times daily
- **Spironolactone 1 to 2 mg/kg twice daily (usually given with furosemide and ACE inhibitor. Also used with digoxin)
- *ACE inhibitor (enalapril 0.5 mg/kg BID, benazapril 0.5 mg/kg BID, lisinopril 0.5 mg/kg or others)
- **Digoxin 0.003 to 0.005 mg/kg twice daily as maximum dose based on lean weight, reduce dose by 25% for extra safety
- **Pimobendan 0.3 to 0.6 mg/kg/day (data indicates good results for DCM, firm conclusions in dogs with degenerative valve disease pending)
- ***Carvedilol 1 to 1.5 mg/kg twice daily (work-up to this dose slowly) once overt failure is controlled (atenolol or metaprolol may be of value) once stable?

TREATMENT GOALS

An important goal is to control heart failure which will then control signs of failure and to decrease the ventricular response rate (heart rate). The latter is linked to the degree of sympathetic drive and this is greater with overt congestive heart failure (including signs of dyspnea). The desired slowing of the heart rate to a target range must be decided upon. This range is determined by breed, size and disease (rate may need to be higher than that for lone atrial fibrillation). For example a target heart rate goal would be a range between 90 and 120 bpm. Some dogs may need a target range that is 100 to 150 bpm but studies to know the ideal range are not available.

MONITORING

Monitor respiratory and heart rate at home may be possible with many owners by teaching them to take the heart rate with a stethoscope. Also, monitoring of overall well-being (appetite etc) is important. The following details the specific monitoring for controlling heart rate using the ideal way, which is with 24-hour Holter monitoring.

1. Ideal monitoring for heart rate is 24-hour Holter monitoring repeated 7 to 10 days after beginning treatment and recheck parameters listed and assess for meeting target range
2. Adjust drug doses up or down to titrate the need to control fluid retention and heart rate
3. Recheck chemistry panel for renal function and electrolyte status 10 to 14 days after beginning medication
4. Check digoxin levels 8 to 12 hours after pilling 10 to 14 days after beginning medication. Repeat as needed.

5. Ideal to recheck thoracic radiographs and electrocardiogram at the time of the second Holter recording to assess heart rate response.
6. If the initial heart rate is more than 200 bpm, vigilant follow-up within one week is ideal with home monitoring on the days before this examination. Dogs with heart rates of greater than 200 bpm frequently require combination therapy.

CONTROVERSIAL POINTS

There are many controversial points with regards to the treatment of congestive heart failure and the specific drugs selected. The following are some controversial points.

1. Treatment with beta-adrenergic blockers is controversial at this stage of failure and may actually be contraindicated until failure is well controlled.
2. Treatment with pimobendan by initial studies shows promise for DCM, but the benefit for degenerative valve disease is unknown, although in the late stages of endocardiosis the disease is likely very similar.
3. The exact target heart rate for various breeds with different diseases and stages of failure is unknown. The recommendations here are only initial suggestions that need further evaluation and critical review.
4. Some people no longer like to use digoxin.

MANAGEMENT OF VENTRICULAR ARRHYTHMIAS

The treatment of ventricular arrhythmias (VA) has dramatically changed over the last 30 years in human medicine. Reading this literature and more critically evaluating our standard of care in dogs also has altered our approach to the management of VA. Decades ago recommendations for the treatment of VA revolved around the number of premature complexes identified by routine electrocardiography (ECG), but today treatment is reserved for VA that are judged to be truly 'dangerous.' Furthermore, the success or failure of long-term treatment is more critically studied by 24-hour ambulatory ECG monitoring (Holter monitoring). In this discussion the following will be addressed in practical terms discussing the medications that are available to most practitioners: (1) when should VA be treated (2) what are the most common diseases or circumstances that demand treatment, (3) what determines route of administration [intravenous (IV) versus oral (PO)] and what medications should be selected, and (4) how should the VA be monitored during therapy.

Ventricular arrhythmias should be treated when they result in clinical signs, tachycardiomyopathy or harbor the risk of death. Hemodynamic consequences of VA that cause clinical signs are related to hypotension. Sustained hypotension causes weakness, lethargy, exercise intolerance and, if severe and prolonged, syncope. The development of low systemic blood pressure that persists long enough to result in clinical signs is primarily related to ventricular tachycardia (VT) that is rapid and prolonged (sustained), and not to single or paired ventricular premature complexes. It is possible that the latter can lead to ventricular fibrillation (VF) when such beats fall within the vulnerable period of the T wave. This is known as R on T phenomenon. Although such timing of a premature complex can induce VF, how frequently this occurs in the dog has not been ascertained. Thus, the criterion to define the R on T interval that requires treatment in the dog is unknown. Polymorphic VA also have traditionally been viewed as more ominous than monomorphic VA; however, this is not necessarily true. Boxers with arrhythmogenic right ventricular cardiomyopathy (ARVC) 85% of the time have monomorphic VT and their risk of sudden death is high. Older dogs with mitral regurgitation can have single ventricular premature complexes that are polymorphic and for which the frequency of sudden death is low. In contrast, Doberman pinchers with dilated cardiomyopathy (DCM) do have polymorphic VT and a high incidence of sudden death. Therefore, the assessment of risk depends on the incorporation of multiple factors for each patient. It should be emphasized in this appraisal, underlying cardiac disease must be considered in addition to type of VA present. Animals can tolerate sustained and rapid VT for more prolonged periods if they have adequate myocardial function and are capable of compensating (eg, baroreceptor reflex) for the VT. Therefore, when there is underlying myocardial failure (eg, DCM, ARVC, substantial AV valve regurgitation) the need to suppress the VT is more important; however, because of additional physiologic issues like renal perfusion and concurrent drug medication, the treatment is more challenging. Importantly, when a tachyarrhythmia persists structural and electrical remodeling can develop that can be detrimental and actually induce myocardial failure. This has been proven experimentally in the dog and recognized clinically. That is, a dog that initially only has a tachyarrhythmia without myocardial failure will develop such if the rapid rate is not control. The myocardial failure can be permanent if the arrhythmia persists for a number of weeks or even days if the rate is very fast. Therefore, again, one of the major determinants of risk and need to treat rests in the rate of the arrhythmia. The faster and more sustained the arrhythmia, the more aggressive the treatment must be.

By examining the natural history of a diseases or the circumstances that are associated with VA, those that most often result in clinical signs or sudden death can be identified. Likely the two most common diseases that demand treatment for VT are ARVC in boxers and DCM in Doberman pinchers (and other afflicted breeds). Another breed with sudden death related to VT is the German shepherd. The most common circumstances that cause VT are traumatic myocarditis, myocarditis, and gastric torsion/volvulus.

The VT identified in boxers is most frequently rapid (rates exceed 250 bpm), monomorphic, and it is of a left bundle branch block pattern with an upright orientation in leads II, III, and aVF. Holter recordings have documented that often the VT that causes clinical signs occurs when the dogs are excited or exercising. The latter circumstances which are associated with increases in sympathetic tone are often the triggers for the VT. Importantly, controlling the triggers of arrhythmias can be as important in treatment as therapy to disrupt the substrate or mechanism of the arrhythmia. The mechanism of the VT in boxers is unknown. However, the origin of the VT, based on the morphology and the location of the pathology, is from the right ventricle. Recent studies raise the question of disruption of the intercalated disc proteins in affected boxers that could be an arrhythmogenic substrate. Boxers with polymorphic VA often have heart failure, while it is common to see rapid monomorphic VT in boxers with syncope alone. Also, Holter recordings of syncopal boxers has shown that in addition to the VT, some dogs have sinus pauses of greater than 8 seconds that are responsible for the clinical signs. Thus, treatment must be tailored to both arrhythmias. Studies do not exist to prove that treatment of the VT in boxers actually decreases the risk of death; although some work does support the use of certain drugs for the antiarrhythmic effect. Notably, just because a drug decreases the frequency of an arrhythmia, this does not insure that it will prevent sudden death.

Doberman pinchers with VA demanding treatment almost always have concurrent severe myocardial failure due to DCM. This is in contrast to the boxer. The polymorphic VT documented in Doberman pinchers may not be the cause of death as bradyarrhythmias have been documented as another fatal rhythm. Because these dogs are usually on numerous concurrent medications and their hemodynamic status is more fragile, the negative inotropic effect of the antiarrhythmic drug must be considered. Most ventricular arrhythmias are markedly affected by elevations in sympathetic tone and circulating catecholamines, and thus, often antiarrhythmics are either combined with beta-adrenergic blockers (mexiletine plus atenolol) or adrenergic blockade is a component of the specific drug (sotalol, amiodarone) used. In the Doberman pincher titrating the dosage of the drug to have an appropriate antiarrhythmics effect with the least negative inotropic consequence is difficult. In general the comments here apply to other breeds afflicted with DCM.

At first it may seem obvious how to determine whether IV medication is required; however, this is not always true and the wishes of the owner may not permit hospitalization. Dogs with VT and severe systemic hypotension that cause them to be moribund, weak, or repeatedly collapsing require IV treatment with the goal of conversion to sinus rhythm or slowing of the rate. Sometimes dogs in dire distress may be cardioverted if synchronization with the R wave is possible to avoid shocking on the T wave. Regardless of the type of VT, underlying disease or mechanism; lidocaine is the most common drug given IV for the treatment of VT in dogs today. The most common sequence of events is to administer one or several boluses of lidocaine at 1 to 2 mg/kg IV and follow this with a constant rate infusion (CRI) of lidocaine at 40 to 80 µg/kg/min. Most frequently CRI doses approximating 50 to 60 µg/kg/min are required to assure effectiveness. Caution should be used if the total bolus dosage approaches 6 mg/kg over a 15- to 30-minute period of time. Toxicity is recognized as twitching or seizures. Because the half-life of lidocaine is short the side effects dissipate rapidly, but IV diazepam might be required. The most common reason for lidocaine toxicity is miscalculation of the dose in terms of decimal point location. Consequently, clear written instructions with sample doses for the size of the animal are ideal for checking calculations in the emergency situation. Although lidocaine is the most commonly used drug, some prefer to use procainamide IV as a bolus (10 to 15 mg/kg slowly) followed by a CRI (25–50 µg/kg/min). This drug is uncommonly used PO, but still remains as a possible drug for critical VT. Bolus treatment must be delivered with a slower push than lidocaine because more problems can develop with systemic hypotension, although lidocaine doses produce a momentary drop in systemic blood pressure even in dogs with normal myocardial function.

Because lidocaine has multiple antiarrhythmic mechanisms it can be effective regardless of disease or circumstance. However, when lidocaine is ineffective, understanding the reasons for failure is important and alternate medications are needed. Sometimes the reason for a lack of response is that the dose used is too low; thus, up-titration is important to eliminate this as an explanation for failure. The antiarrhythmic effects of lidocaine are hindered in the presence of hypokalemia or acid-base imbalance. After these examinations, a trial with procainamide is logical. Other drugs can be tried as well, but availability is a major concern. When a drug is selected to treat VT, whether IV or PO and the arrhythmia persists the diagnosis of the rhythm may be incorrect. Although less frequent, wide QRS supraventricular tachycardias should be considered. If additional antiarrhythmic drugs are not available for IV trial, then PO medication and hemodynamic support can be given. Sotalol given PO in such situations has converted dangerous VT in several hours when usual IV medications failed. Finally, some VT rhythms are 'malignant' and will not terminate or slow. This happens with severe myocarditis, myocardial infarction or myocardial neoplasia.

Oral medication is used when the VT is not immediately life-threatening. The definition of life-threatening is determined by both the type of VT and the hemodynamic response of the dog. Some dogs will appear undisturbed by a rapid VT particularly if they have preserved myocardial function and the VT is intermittent. To treat with oral medication will usually suffice; however, there are management issues that are critical to knowing the effectiveness of the drug and the dosage selected (see below). Other dogs may be presented with a history of syncope and the cause is suspected to be intermittent VT based on ECG monitoring and Holter monitoring. The most commonly used drugs given PO today for the treatment of VA are sotalol (2.0 to 2.5 mg/kg BID), mexiletine (4 to 8 mg/kg TID) combined with atenolol (0.5 to 1.0 mg/kg BID), or amiodarone. Amiodarone is commonly used in human medicine; however, thus far in the treatment of dogs with VT the published data has emphasized the problems, with little evidence of effectiveness against the VT. It is vital to comment on the doses given. These are regarded as 'usual' and not exact for a particular patient. Antiarrhythmic drugs and adrenergic blockers must be titrated to effect and with the intent to avoid side effects.

When VT is being treated in the intensive care situation with constant ECG monitoring during IV treatment, effective treatment is ideally identified by conversion to a sinus rhythm. Still, critical evaluation is required if the VT occurs in intermittent runs to be convinced that the drug actually caused the conversion and it was not just by chance. With the advent of greater digital storage capacity on computers, electronic ECGs that continuous record the ECG of a critical patient can be effectively evaluated instead of the 'by chance' paper recording. Selected electronic ECG systems currently available can store one hour of data at a time and then be reset. Likely such system will only improve. When dogs are treated by the IV route a positive response should be seen within minutes to bolus therapy and maintained with CRI. If such treatment is given, and no effect is documented in such a time frame, the medication plan should be reconsidered. After stabilization of the dog with IV treatment, transition to oral medication is required if deemed necessary. For this transition, usually beginning the oral medication approximately 1 to 3 doses before stopping the CRI is effective. There is a cross over time when either excessive medication may cause side effects or too little permits the arrhythmia to return. Importantly, just because a drug is effective IV, does not mean that it will be effective given orally, nor that a drug with similar action will be effective. It is not uncommon to have a dog treated with lidocaine in ICU and then switched to sotalol PO.

To know if a drug is having (1) no effect, or (2) an antiarrhythmic or (3) a proarrhythmic effect, Holter monitoring is required. In order to make this judgment a baseline recording is required. Most often such a recording can be made for 24 hours and treatment started immediately after removing the monitor. However, in some dogs the VT may be too dangerous to permit a full 24-hour recording, although the condition of the dog is not so severe that admission to intensive care for IV treatment is required. For these dogs, the longest baseline recording that is felt to be safe is performed and the animal started on medication after this time. Because it is not known that medication will indeed improve the VT, it can be argued that the baseline is as important as the treatment. The latter is true because some dogs do experience proarrhythmic effects from drugs used as antiarrhythmic medication. Therefore, the standard of care for the treatment of VA is as follows: (1) obtain baseline 24-hour Holter monitor recording in the environment where the medication will be administer (home), (2) treat with the selected medication and dosage, (3) recheck 24-hour Holter recording in 7 to 10 days after questioning to insure compliance, (4) evaluate for change in frequency or severity of the VA and determine if treatment is successful or not. If the VA counts and severity are not altered the dosage of medication is usually increased and then the Holter recording repeated 7 to 10 days later. If the VA are not suppressed then an alternative or additional medication can be given. When combinations of antiarrhythmic drugs are used (eg, sotalol plus mexiletine) caution and close monitoring are absolutely needed to avoid side effects.

Because most dogs undergoing treatment for VT have underlying structural or functional disease monitoring requires attention to these aspects of cardiac function. Thus, additional monitoring with thoracic radiography and echocardiography are common. Moreover, examination of blood chemistry profiles in such cases is warranted. It should be stressed that if an owner reports any problems that are new after a medication has been started, it is wisest to blame the drug first. Assessment of side effects is important and only if a critical approach is taken can serious problems be avoided. The most common problems reported are vague and relate to overall well-being in addition to complaints of anorexia. Other complaints reported include twitching and change in behavior.

HEART FAILURE MANAGEMENT

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The treatment of heart disease in dogs is very controversial. Which drugs to use and when to institute treatment occupy many discussions among veterinary cardiologists. The pros and cons of treatment are supported by some clinical trials and many opinions. Likely there is some truth to most of the views and it is the perspective of the type of patient (type and stage of disease) that is different. Moreover, treatment must be individualized. During this session some of the aspects of cardiac drugs that are not as commonly discussed will be presented as they pertain to treatment. The use of these drugs will be placed into the context of clinical case examples. The most common diseases that are considered in dogs are degenerative valve disease and myocardial failure associated with dilated cardiomyopathy.

Heart failure must be staged in order to adjust treatment. To accurately know the stage or severity of disease is difficult because (1) symptoms are unknown. Only clinical signs can be assessed in animals. Therefore, earlier signs of disease are missed. (2) Variation in tolerance to heart failure or recognition of clinical signs can place an animal in the wrong stage, (3) Diagnostic tests for earlier stages of disease are insensitive to the presence of disease, and (4) no clinical trials to really assess the definitions of staging heart failure exists (repeatability of staging heart failure by trained observers). Therefore, in veterinary cardiology we have adopted in part the staging methods from human medicine and these are not optimal. When the various clinical trials in veterinary medicine are compared, the validity may not be sound for such comparisons because different methods of staging the disease progression were used. The New York Heart Association Classification of Heart Failure is summarized as:

1. Class 1 Heart disease - no symptoms
2. Class 2 Heart disease - symptoms only with vigorous exercise
3. Class 3 Heart disease - symptoms with routine daily activity
4. Class 4 Heart disease - symptoms at rest

Also, an additional classification considered in human medicine was recently developed to complement the NYHA scheme and is summarized as:

1. High risk for heart failure but no apparent structural abnormality of the heart disease
2. Structural abnormality present but no symptoms of heart failure
3. Structural abnormality and current or previous symptoms of heart failure
4. End-stage symptoms and refractory to treatment

An attempt was made to improve the system in canine patients with the International Small Animal Cardiac Health Council Classification of Heart Failure and it is summarized as:

1. Class I – Heart disease is present, but no clinical signs. Abnormalities may be seen by the ECG, radiograph, or echocardiogram.
2. Class II – Some clinical signs are present at rest or with mild exercise.
3. Class III – Clinical signs critical with dyspnea, ascites, and marked exercise intolerance.

In the clinical trials in veterinary medicine there has been a collapsing of the staging and a simplification such that general conclusions may not apply to subgroups and individuals. Often the NYHA classification collapses into two groups of (1) clinical signs or (2) no clinical signs. In some studies the pivotal classification is by thoracic radiographs where by the dog is categorized into 'failure' completely on the basis of the radiographic appearance of pulmonary edema or not. Consequently, this will be an evaluation of severe cardiac decompensation.

The following are drugs that are used in the treatment of heart failure. Following each drug the controversial points are stated.

- **Furosemide.** What dose should be used? Standard recommendations have been made but some advocate much higher doses. Should it only be used with overt edema? Does diuretic resistance exist in the dog? In severely decompensated cases is a constant rate infusion better than boluses?
- **Spironolactone.** Will this old drug help dogs? This is an aldosterone-receptor blocker that is known as a potassium-sparing diuretic. However, it is not for its diuretic effect that spironolactone has gained attention lately, instead it is because of the antifibrotic effect and prolongation of life that has been documented in humans. Some preliminary studies in dogs seem promising. If the use of spironolactone is for its antifibrotic effect, then the diseases that we treat should have fibrosis as a part of the pathology. Further study is needed to know if positive benefits really exist.
- **Inodilators.** The most common drug in this category used to date in veterinary medicine is pimobendan. Another drug in this category is levosimendan. These drugs have two effects: increased calcium sensitivity and increased cAMP activity. The amount of each varies with the specific drug and the dose. A great deal of attention has been given to this class of drugs in recent years. Many persons give positive testimonials to the effectiveness in dogs with systolic dysfunction, yet others warn of its dangers. Studies have indicated that pimobendan has a beneficial effect particularly in dogs with systolic dysfunction. Some dogs with systolic dysfunction can have marked improvement when treated with pimobendan. There is some concern and

controversy about using pimobendan in dogs early in disease when systolic function is not depressed. A recent clinical trial was conducted in Europe to assess the use of pimobendan in dogs with mitral regurgitation. The results of the trial are pending. Other clinical trials evaluating the use of levosimendan are also underway. These drugs are similar, but they do have important differences that may have clinical relevance.

- **Angiotensin enzyme-converting inhibitors (ACEI).** Strong opinions have been voiced concerning the use of ACEI without pulmonary edema. When should this group of drugs be used? Is there any difference between the various types of ACEI? Is there a way that all the clinical trial is actually compatible? ACEI drugs decrease serum ACE activity and aldosterone levels, but increase plasma renin activity. Some of the –pril drugs may have more effect on the local ACE system than the systemic. Some are prodrugs demanding conversion by the liver to the active form and some are secreted more by the kidneys than metabolized by the liver. These drugs do have different durations of action and so this is an important point in medicating the patient as to the interval of dosing.

    - Enalapril (Vasotec)
    - Lisinopril (Zestril, Prinivil)
    - Benazepril (Lotensin)
    - Quinapril (Accupril)
    - Ramipril (Altace)
    - Fosinopril (Monopril)

ACEI drugs are given to decrease the RAAS system. This will decrease aldosterone which then decreases sodium retention and consequently water retention. Also high aldosterone levels cause excretion of potassium and can mediate with angiotensin II inflammation and fibrosis along with causing a loss of baroreceptor response. But there are other means by which aldosterone is elevated that 'fight' this counter action of the ACEI drugs. These include catecholamines, endothelin I, and arginine vasopressin (ADH). Do clinical trials support the use of ACEI in heart failure? Most trials support the use of ACEI in dogs, particularly when heart failure is present and most likely when there is evidence of cardiomegaly. Some breeds may have different responses to ACEI. Moreover, ACEI are not started in dogs that have minimal disease and no cardiomegaly.

- Positive inotropes (eg, digoxin). Some cardiologists do not believe in digoxin. Others do believe that it can help patients. The differences of opinions mean that there are likely more than one way to treat heart failure and one path of therapy includes digoxin, while another path does not. There are some positive actions of digoxin that support its use. These include restoring restores autonomic balance, mild positive inotrope, inhibition of rennin, and decreasing sinus heart rate and ventricular response in atrial fibrillation (AF) which is common in heart failure. To effectively control heart rate in AF it is often necessary to use drugs such as long-acting diltiazem in conjunction with digoxin. Digoxin is used orally and not intravenously today. The dose is lower than what has been used in the past. Currently, we are using 0.003 mg/kg twice daily based on LEAN BODY WEIGHT. Also, our serum level that we strive for to say that the animal is titrated to the dosage that we desire is lower than what it has been in the past. We use approximately 0.7 to 1.0 ng/dL as our target range. The older range was 1 to 2 ng/dL, but this caused more adverse clinical signs.
- **Antiarrhythmics for common arrhythmias seen in heart failure.** The most common arrhythmia treated is atrial fibrillation. A point that needs to be emphasized is the use of 24-hour ECG (Holter) monitoring for the assessment of the heart rate and rhythm in atrial fibrillation.
- **Beta-adrenergic blockade.** The use of this category of drugs is the one that has the least clinical experience despite the theoretical reasons that we should use beta-blockers early in disease. The three most common are carvedilol, bisoprolol, and metoprolol.

When treating animals with heart failure we usually do not use a single drug. Heart failure must be attacked from different angles given the complexity. There are different ways to 'attack' and this is likely why different combinations of drugs can work. Some of the most common combinations include the following. Be aware that the way that we treat heart failure is evolving and changing. This is because we do not have a perfect method to solve the many problems.

FAINTING: BAD HEART OR BAD BRAIN?

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Sudden episodic collapse may be associated with many disease conditions, but cardiovascular or neurologic diseases are the most common etiologies. Most often, the patient is fully recovered at the time of examination and may never manifest the collapsing behaviors in the presence of the clinician. Despite the episodes typically causing great consternation in the clients observing them, the clients are often unable to accurately describe the incident, are at a loss for critical details and may offer information that tends to cloud the picture rather than illuminate it. In these situations, prioritization of differential diagnoses and development of a diagnostic plan may be difficult.

The most important parts of the investigation occur before any diagnostic tests are performed. Because the patient frequently will not demonstrate the behavior in front of the clinician, the pertinent information must come from the owner of the pet (through the history) and from the pet itself (through observation and physical examination). Analysis of the signalment, history and physical examination (PE) findings will determine what type of further testing is required and the logical order of the tests.

DIFFERENTIATION OF SYNCOPE AND SEIZURE

Syncope is often defined as transient loss of consciousness accompanied by loss of postural tone and associated with a spontaneous recovery. Typically, there is little warning other than a brief moment of dizziness or nausea, the episode usually lasts < 1 minute and recovery to normality or near-normality occurs within minutes. During the event, the observer may describe their pet as limp or stiff ("all stretched out"), but there is no repetitive motion reported in most cases. In contrast, a seizuring animal typically exhibits motor activity during the event (i.e. paddling, scrabbling motions, chomping, drooling). Prodromal events associated with seizures may precede the event by minutes to days, and often include behavioral changes, which may be predictable enough to "warn" observant owners that an event is coming. After the seizure event (which may have required medical therapy to terminate), recovery may be prolonged, with animals showing behavior changes or disorientation for minutes to hours. Event duration of more than 3 minutes is more consistent with seizure than syncope.

History: What Can The Event Observer Tell Us?

Before a specific history regarding the event is taken, it is helpful to quickly review the patient's general health with the owner, with particular and meticulous attention to concurrent diseases and therapies for those diseases. In elderly patients on multiple medications, especially cardiovascular medications, drug-related orthostatic hypotension is a common cause of episodic weakness or syncope. The risk of hypotension in patients receiving diuretics and vasodilators is exponentially increased if the patient is not eating well or is anorexic.

The core of event investigation is the description of the event. The best information regarding the circumstances and substance of the event comes from a direct observer. If the observer is not present at the consultation, a phone call to the observer during or after the examination is needed. After recording a full spontaneous description of what the observer saw during the event, the clinician can elicit further details with a few focused, precise questions. These questions should be asked regardless of whether the initial description appeared to "cover" the information. Questions of limited scope that direct attention to one particular aspect of the event frequently allows the observer to recall details lost in the excitement of the overall event. In addition, the observer may not be aware that certain details are important until asked. Examples of focused questions that may be helpful are presented in Table 1.

Physical Examination: What Can The Patient Tell Us?

The signalment of the patient, particularly the breed (primarily dogs) and age (dogs and cats) can be very helpful in directing the subsequent investigation. Idiopathic epilepsy or congenital heart diseases like pulmonic stenosis are most commonly diagnosed in young animals, and certain breeds may be more likely to be affected with certain anomalies. In cases of syncope, some breeds of dogs (Doberman pinschers, Boxers, Schnauzers) have an increased incidence of cardiac diseases commonly associated with syncope-inducing arrhythmias.

Beyond observations of signalment, a thorough physical examination (PE), including retinal examination, is mandatory. Once a general PE is complete, a second, more specific examinations focusing on the cardiovascular and central nervous systems are performed. Any evidence of cardiovascular abnormality, including abnormal heart rate or heart rhythm, detection of extra heart sounds or murmurs, or detection of poor perfusion via palpation of weak peripheral pulses or observation of abnormal capillary refill time is an indication for further investigation of the cardiovascular system. Findings that focus attention on the central nervous system as the cause of the event in question include findings of intracranial lesions (focal cranial nerve deficits, mentation changes) or evidence of hypertension (retinal vascular congestion, retinal hemorrhage or detachment).

APPROACH TO THE PATIENT WITH SYNCOPE OR SEIZURE

A thorough history and PE should be completed on *every* patient presented for evaluation of a sudden collapse event. Although findings of these two important examinations usually categorize events as syncope or seizure and guide further testing in most cases, there are few important exceptions. Right to left cardiac shunts

Table 1. Focused Questions for Observers of Sudden Collapse Events

Question	Syncope	Seizure
What was the pet doing when the event occurred?	• Activities involving exertion, straining (urination, defecation, cough), stress or sudden pain was involved, syncope is more likely. • Not associated with rest or sleep.	• Any activity or none (rest/sleep)
What was the posture/degree and type of motion of the pet during the event?	• Limp/motionless • Stiff/motionless	• May show "classic" paddling/chomping behavior, head bobbing, drooling • Movements may be misconstrued as "trying to get up"
Did the pet look at you when you called his/her name?	• During syncopal event, no recognition, sudden return to responsiveness. • Presence of recognition may indicate weakness rather than syncope.	• During event, no evidence of recognition • Return to full responsiveness may be slow
How long did the event last?	• 1-2 minutes	• Any length, but event length > 3 minutes is likely seizure rather than syncope

leading to polcythemia may cause either seizures (if PCV > 75%) or exertional syncope (when right-to-left shunting is exacerbated by decreased peripheral resistance during exercise). Occasionally, prolonged hypoxia during syncope may result in seizure activity ("convulsive syncope") and some partial seizures appear as syncope ("temporal lobe syncope"). The latter two exceptions appear to be rarely noted in veterinary patients.

General Approach to Suspected Seizure

Patients with evidence of intracranial disease on PE can be investigated further with imaging (eg, MRI) or evaluation of cerebrospinal fluid. Seizuring patients should also be investigated for metabolic causes of seizures, including biochemical disturbances and polycythemia. If metabolic derangements leading to seizures are discovered, a thorough investigation of the underlying cause is indicated. Lastly, patients with a history of seizures should have their systemic blood pressure (BP) evaluated for evidence of systemic hypertension. The most common overt clinical sign of severe systemic hypertension is intraocular or retinal hemorrhage or retinal detachment, but systemic hypertension may also be associated with intracranial hemorrhage or edema that may lead to seizures. Since this evaluation is aimed at identifying hypertension as the underlying cause of seizures, BP measurement should be performed when the animal is clinically normal (ie, not immediately following the event).

General Approach to Suspected Syncope

Examination of patients suspected of syncopal events begins with the careful history and PE detailed above. In addition, ALL patients with syncope should have a resting electrocardiogram (ECG) recorded, regardless of auscultation findings. In some cases, abnormal rhythms responsible for syncope may have a normal heart rate by auscultation. In addition, ECG recordings may reveal evidence of cardiac disease (eg, conduction disturbances) even if overt arrhythmias are not detected. Evaluation of BP in patients with collapse events, especially those receiving cardiovascular medications, is also routinely recommended. A complete cardiac assessment is indicated when any of the above findings are abnormal (auscultation, ECG, BP) or reveal concurrent disease or medications likely to affect blood pressure. Common cardiovascular causes of syncope are outline in Table 2.

RATIONAL DIAGNOSTIC TESTING FOR PATIENTS WITH SUSPECTED CARDIOVASCULAR SYNCOPE

Once the initial cardiovascular PE, ECG, and BP evaluation are completed, thoracic radiographs and an echocardiogram are recommended to diagnose or exclude cardiac disease from the list of possible etiologies. If a significant cardiac abnormality/disease is identified, that abnormality should be addressed first and thoroughly, and any pre-existing medications should be reviewed and their possible contribution to the problems evaluated.

Ambulatory Electrocardiography

The possible contribution of arrhythmias to the genesis of syncopal events can be further investigated through the use of ambulatory electrocardiography:

- **Telemetry observation:** Hospitalized patients may be monitored with telemetric electrocardiography

Table 2. Common Cardiovascular Causes of Syncope

Cause	Comment
1. Sudden decrease or loss of cardiac output	
• Arrhythmia	
• Bradyarrhythmias	Sinus arrest, 2nd /3rd degree heart block
• Tachyarrhythmias	• Supraventricular or ventricular tachycardia
• Obstruction to outflow	
• Pulmonic stenosis	• Most common with severe pulmonic stenosis
• Pulmonary hypertensio	• Syncope may be the only presenting clinical sign
• Aortic stenosis	• Most common with severe stenosis. • Syncope may also be due to ventricular arrhythmias
• Pulmonary thromboembolism	• Typically accompanied by dramatic dyspnea
• Inadequate preload (ventricular filling pressure)	
• Cardiac tamponade	• In the presence of severe pericardial effusion or moderate pericardial effusion if abnormal pericardial sac or concurrent dehydration
• Mitral or tricuspid stenosis	
• Extreme dehydration	• May be secondary to overuse of diuretics • May be complicated by electrolyte abnormalities
• More complicated and rare congenital malformations	• E.g. cor triatriatum dexter or sinister
2. Situational hypoxia	
• Pulmonary edema (congestive heart failure)	Usually responsive to resolution of pulmonary edema
• Pulmonary thromboembolism	• Typically accompanied by dramatic dyspnea
3. Inadequate BP with normal cardiac output	
• Drug-related hypotension	• More of a problem in elderly patients
• Neurally-mediated syncope	• Diagnosis of exclusion
• Autonomic abnormalities associated with severe systemic diseases	• E.g. sepsis, neoplasia

during the hospitalization; the ongoing tracings are monitored for suggestive or diagnostic abnormalities

- **Holter recorders:** Portable monitors worn by the patient in a harness or bandage; most monitors record approximately 24 to 48 hours of electrographic information. Most helpful in patients in whom events are frequent or information regarding the total number of arrhythmias in 24 hours is needed.
- **Event monitors:** portable monitors that are worn for an extended period of time and are activated by the owner when an event is observed. Helpful for infrequent events and to exclude arrhythmia as a cause of events.
- **Implantable recorders (eg, Reveal™):** Digital ECG recorders that are implanted subcutaneously over the heart. These recorders are well tolerated and may be left in place indefinitely (or until the end of battery life). Sample ECGs are recorded automatically when an abnormal rhythm is sensed, or the recorded may be activated by the owner during an event. The data is downloaded with an external "wand" sensor held just above the skin over the monitor. Availability of these monitors for veterinary use is limited at present.

Table 3. Recommendations for Further Testing in Syncopal Patients

Results of Cardiovascular Testing	Recommendations
• Results of basic testing reveals clear rhythm abnormality	• Treat underlying arrhythmia
• Results of basic testing reveals structural heart disease with or without heart failure	• Rule out complicating arrhythmias, treat as needed • Optimal therapy of heart disease/failure
• No abnormalities on auscultation, resting ECG or BP assessment • Canine patient is not an "at-risk" breed*	• If first time event and patient is clinically normal, consider monitoring over time with client counseling regarding "what to watch for" • If events are recurrent, consider event monitor
• Canine patient is "at risk" breed* • No abnormalities on auscultation, resting ECG or BP assessment	• Ambulatory ECG monitoring strongly recommended
• Cardiovascular disease is present • Hypotension is present • Cardiovascular medications are in use	• Assess and address hydration and electrolyte abnormalities • Address cause(s) of anorexia, if present • Temporarily discontinue or alter doses of medications as needed

*Doberman pinscher, Boxers

Recommended reading available from author on request.

A PRACTICAL APPROACH TO ACID–BASE ABNORMALITIES

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Acid–base disorders are COMMON in critical illness. Arterial and venous blood gas analysis provides the veterinary health care team with rapid access to valuable diagnostic information about their patients. Coupled with a complete medical history, full physical examination, electrolyte profile, packed cell volume (PCV), total solids (TS), glucose, and blood urea nitrogen (BUN), determination of the acid–base abnormalities present in an individual can rapidly narrow the list of differential diagnoses for the underlying medical problem(s) facilitating a rapid movement towards focused diagnostic testing and therapeutic intervention.

Recent technological advances have brought affordable blood gas, electrolyte, lactate, blood glucose, ACT, and creatinine analysis to veterinarians in a point-of-care setting.[a,b] This article provides the reader with an introduction to blood gas analysis for determining the acid–base status of the patient presented with critical illness.

SAMPLING

Arterial blood gas samples are required for determining all aspects of the patient's acid–base and respiratory status. Venous blood gas specimens will provide information surrounding the metabolic side of the patient's acid–base status, but cannot be used as a substitute for arterial blood gas analysis (described below), nor can it be used for calculation of pulmonary function parameters such as the alveolar–arterial oxygen tension gradient. This being said, the author frequently acquires venous blood gas data coupled to electrolyte, and other chemical analysis (BUN/lactate) in many patients presenting with critical illness not affecting the respiratory system. When coupled with a PCV/TS/blood glucose, venous blood gas/electrolyte analysis/ biochemical analysis provides the attending clinician with an excellent database that will enable him or her to immediately narrow the list of differential diagnoses and make appropriate therapy decisions while directing additional diagnostic testing.

Specimens collected for arterial or venous blood gas analysis must be kept anaerobic. This is accomplished by removing all air from the sampling syringe and then using a stopper or provided cap to seal the tip of the needle or syringe, respectively.

Samples for venous blood gas analysis may be taken from any vein. The most commonly utilized sites are the jugular, cephalic, and saphenous veins. Sampling of blood from the arterial system is an acquired skill that requires practice to perfect. The most commonly sampled sites are the dorsal pedal (metatarsal) and femoral arteries. Caution should be exercised and samples should not be taken from the femoral artery or the jugular vein in patients with moderate to severe hemostatic abnormalities or evidence of spontaneous hemorrhage.

A strong knowledge of regional anatomy is the key to sampling from the dorsal pedal artery. The dorsal pedal artery crosses from lateral to medial (very superficially) just below the tarsus where it then travels between metatarsals II and III (Figure 1). The most distal site at which the artery can be palpated is optimal for sampling. This location is usually where the artery dives between metatarsals II and III (see circle in Figure I). Equipment necessary for sampling from the dorsal pedal artery is an arterial blood gas syringe[c] or a preplaced arterial catheter. Arterial blood gas syringes are vented, making it unnecessary for the clinician to aspirate the plunger while sampling. Sampling can be performed with a heparinized syringe (aspirate heparin into syringe and evacuate as much as possible), but the procedure is much more challenging because the syringe must be aspirated. The procedure for sampling from the dorsal pedal artery is as follows:

1. Position the animal in lateral recumbency with the limb to be sampled down.
2. Clip the hair from the area and apply a full surgical scrub.
3. Have an assistant place a few fingers behind the hock to help immobilize it. Pressure should NOT be applied around the circumference of the hock.
4. Wear gloves and palpate the dorsal pedal artery along its entire course.
5. Insert needle (25- to 22-gauge) through skin just distal to the site at which the artery can be palpated at the angles indicated in Figure I. Keep in mind that the artery is very superficial.
6. Advance the needle firmly in 1mm increments until blood is noted in the needle hub.
7. Once blood is seen in the hub, immobilize the syringe.
8. The syringe should fill in 5 to 10 seconds (depending on the size of the patient and the size of the sample acquired).
9. Withdraw the needle and apply a compressive dressing for 10 to 15 minutes.
10. Handle sample anaerobically and analyze sample immediately.

BLOOD GAS ANALYSIS; ANSWER THE QUESTIONS!

When beginning to work through an acid-base problem, it is first important to recognize that there are three main chemical "players" that largely determine the pH of the blood. These include hydrogen ion ([H+]), the partial pressure of CO_2 dissolved in the arterial blood ($PaCO_2$), and bicarbonate (HCO_3). Hydrogen ion should be considered a fixed acid and will thus promote acidemia, $PaCO_2$ should be considered a volatile acid and will also promote acidemia, while bicarbonate should be considered a base and will promote alkalemia. [H+] and bicarbonate concentration are largely regulated

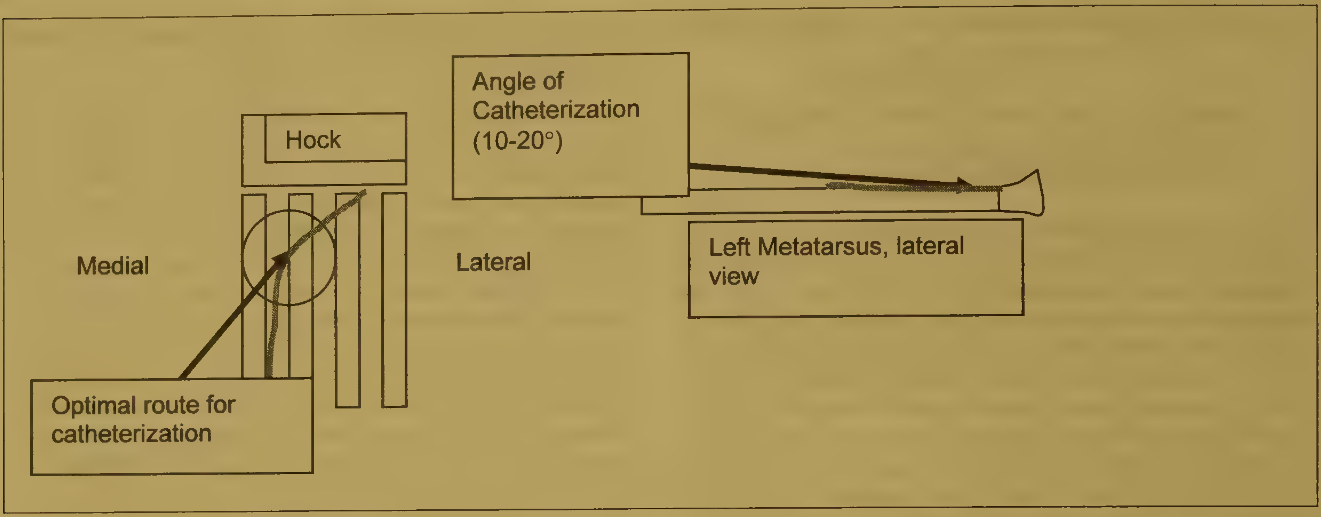
Hock
Angle of Catheterization (10-20°)
Medial
Lateral
Left Metatarsus, lateral view
Optimal route for catheterization

Figure I. Dorsal pedal arterial anatomy (left hind limb)

by the kidneys while $PaCO_2$ is regulated by the respiratory system through ventilation. When evaluating an arterial blood gas, the bicarbonate concentration will tell us about the metabolic side of our acid–base problem while the $PaCO_2$ will tell us about the respiratory side of our acid–base problem.

Normal biologic processes function best around a neutral pH (7.35–7.45). As a result, the pH of the blood is tightly regulated around a pH of 7.4. When the pH deviates due to a pathologic process, compensatory mechanisms come into play to minimize the change and to compensate for it. The respiratory system can rapidly compensate for metabolic abnormalities and the renal system is able to compensate over time for respiratory acid-base abnormalities.

Despite the normal pH ranging from 7.35–7.45, for the purposes of acid–base analysis, normal pH will be considered 7.40. Patients with a pH less than 7.4 are acidemic and those with a pH greater than 7.4 are alkalemic. Normal bicarbonate concentration will be considered to be 22mEq/L and normal $PaCO_2$ will be considered 35 mmHg.

The acid–base disturbances and the compensatory change that occurs are shown in Table 1. Table 2 demonstrates appropriate compensation for a given acid–base disturbance.

Answering the following three questions will facilitate the diagnosis of the underlying acid–base problem from which a list of differential diagnoses can be formulated such that additional diagnostic testing can be directed to make a definitive diagnosis.

Table 1. Acid–Base Disturbances and the Compensatory Change that Occurs

Disturbance	**pH**	**Mechanism**	**Compensatory Response**
Metabolic Acidosis	↓	↓ HCO_3 / ↑ [H+]	↓$PaCO_2$ (Hyperventilation)
Respiratory Acidosis	↓	↑$PaCO_2$ (Hypoventilation)	↑HCO_3
Metabolic Alkalosis	↑	↑HCO_3 / ↓[H+]	↑$PaCO_2$ (Hypoventilation)
Respiratory Alkalosis	↑	↓$PaCO_2$ (Hyperventilation)	↓ HCO_3
Mixed Disturbance	↑ or ↓	Variable	Variable

Table 2. Appropriate Compensation for a Given Acid-Base Disturbance

Disturbance	**Expected Compensatory Response**
Metabolic acidosis	Exp. P_aCO2 = 35 – [(22 – HCO_3) X 0.7]+/-3 mmHg
Metabolic alkalosis	Exp. $PaCO2$ = 35 + [(HCO_3 – 22) X 0.7]+/-3 mmHg
Respiratory acidosis (acute <24 hr)	Exp. HCO_3 = 22 + [(P_aCO_2 – 35)X0.15]+/-2 mEq/L
Respiratory acidosis (chronic >24 hr)	Exp. HCO_3 = 22 + [(P_aCO_2 – 35)X0.35]+/-2 mEq/L
Respiratory alkalosis (acute <24 hr)	Exp. HCO_3 = 22 – [(35 – P_aCO_2) x 0.25]+/-2 mEq/L
Respiratory alkalosis (chronic >24 hr)	Exp. HCO_3 = 22 – [(35 – P_aCO_2) x 0.55]+/-2 mEq/L

Question 1: What is the pH?

There are five possible acid–base abnormalities (metabolic acidosis, metabolic alkalosis, respiratory acidosis, respiratory alkalosis, mixed disturbance). Determination of the pH will narrow the possibilities to three. The primary acid–base disturbance has to be one that causes the pH to move in the given direction. For example, if the pH is 7.25, then the primary acid–base disturbance has to be one that causes acidemia. These include metabolic acidosis, respiratory acidosis, and a mixed disturbance. Conversely, if the pH is >7.40, then the primary acid–base disturbance must be metabolic alkalosis, respiratory alkalosis, or a mixed disturbance.

Question 2: Which direction have the bicarbonate and the $PaCO_2$ moved?

Remember that normal bicarbonate concentration is considered 22mEq/L and normal $PaCO_2$ = 35 mmHg. Remember that bicarbonate tells us about the metabolic side of our acid–base equation and behaves like a base and that $PaCO_2$ tells us about the respiratory side of our acid-base equation and behaves as a volatile acid. Table 3 describes how changes in $PaCO_2$ and bicarbonate tend toward specific acid–base disturbances.

If, for example, the patient's pH is 7.25, he is acidemic. If the bicarbonate is low, this would imply that part of his acid–base problem is metabolic acidosis. If the $PaCO_2$ is also low, this would imply that he also has respiratory alkalosis. Because the pH is low, the PRIMARY acid–base disturbance must by metabolic acidosis (or mixed). Question number 2 will effectively narrow the list of possible acid-base disturbances to two (from an original of five possibilities).

Question 3: Is appropriate compensation occurring?

As mentioned previously, deviation of the pH from normal is minimized through compensatory responses. Equations (see above) have been developed that describe appropriate levels of compensation for given acid–base disturbances. If the compensatory change is in excess of or smaller than the expected change (or in the opposite direction of the expected change), a mixed disturbance is present. With completion of question 3, the acid–base problem is solved.

EXAMPLE

There is no better strategy for perfection of acid-base problem solving than to practice. The following example illustrates solving of a common clinically encountered acid-base problem. This arterial blood gas sample is collected from a 9-year-old female spayed mixed breed dog that presents with the complaint of acute collapse.

pH: 7.27
$PaCO_2$: 27 mmHg
HCO_3: 12 mEq/L

Question 1: What is the pH?

The patient is acidemic. Thus, the primary acid–base disturbance must be metabolic acidosis, respiratory acidosis, or a mixed disturbance.

Question 2: Which direction have the bicarbonate and the $PaCO_2$ moved?

The bicarbonate is low (a deficit of base). Bicarbonate tells us about the metabolic side of our acid–base problem. The low bicarbonate suggests that a component of our acid–base disturbance is metabolic acidosis.

The $PaCO_2$ is also low. $PaCO_2$ tells us about the respiratory side of our acid–base problem and because $PaCO_2$ behaves as a volatile acid, a low $PaCO_2$ suggests that a component of our acid-base problem is respiratory alkalosis.

Because the pH is low, metabolic acidosis must be the primary acid–base disturbance. However, a mixed disturbance is also possible.

Question 3: Is appropriate compensation occurring?

The compensatory response for metabolic acidosis is hyperventilation (respiratory alkalosis). Our patient appears to be hyperventilating (as expected). Choosing the equation

$$(\text{Exp. } P_aCO_2 = 35 - [(22\text{-}HCO_3) \times 0.7] \pm 3 \text{ mmHg})$$

that describes the expected change in $PaCO_2$ for the decrease in bicarbonate seen in a metabolic acidosis reveals that the expected range of $PaCO_2$ in this patient is 25 to 31 mmHg. Our patient's $PaCO_2$ is within the expected range. Thus, the diagnosis for this acid–base problem is metabolic acidosis. Had the $PaCO_2$ been <25 mmHg or >31 mmHg, a diagnosis of a mixed disturbance would have been made. A list of possible differential diagnoses for a dog that presents with metabolic acidosis is shown in Table 4.

A complete medical history and full physical examination coupled with basic ancillary diagnostic tests often reveal the specific etiology for a given acid–base disturbance.

Table 3. Changes in $PaCO_2$ and Bicarbonate and Specific Acid–Base Disturbances

Change	Acid-Base Abnormality	Why?
$PaCO_2$ > 35mmHg	Respiratory acidosis.	Retention of volatile acid.
$PaCO_2$ < 35mmHg	Respiratory alkalosis.	Blowing off volatile acid.
HCO_3 > 22mEq/L	Metabolic alkalosis	Retention of base.
HCO_3 < 22mEq/L	Metabolic acidosis	Use (buffering) / loss of base.

Table 4. Differential Diagnoses for Specific Acid–Base Disturbances

Acid–Base Disturbance	Etiology / Differential Diagnoses
Metabolic acidosis	▪ Lactic acidosis ▪ Diabetic ketoacidosis ▪ Failure to excrete [H+] as is seen in renal failure and hypoadrenocorticism ▪ Ethylene glycol metabolites and aspirin toxicity
Metabolic alkalosis	▪ GI obstruction oral to the major duodenal papilla ▪ Vomiting ▪ Gastric suctioning ▪ Furosemide therapy
Respiratory acidosis	▪ Hypoventilation (various causes)
Respiratory alkalosis	▪ Hyperventilation (various causes)

FOOTNOTES

a. i-STAT Handheld Clinical Analyzer; Heska Corporation. Fort Collins, CO.
b. VetStat Electrolyte and Blood Gas Analyzer; IDEXX Laboratories, Inc. Westbrook, ME
c. Sims Portex Pro-Vent; Smiths Medical. London, UK.

APPROACH TO THE HEAD TRAUMA PATIENT

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PATHOPHYSIOLOGY OF HEAD TRAUMA

Traumatic brain injury (TBI) in the small animal patient may occur subsequent to a number of traumatic events including, but not limited to human–animal interactions, motor vehicle accidents, projectiles, animal–animal interactions, and falls from a height. Primary injuries result from a variety of forces (acceleration, deceleration, torsion, etc.) imparted upon the cranium and its contents and may range from mass lesions caused by vascular disruption (epidural hematoma, subdural hematoma, intraparenchymal hemorrhage) to contusions and diffuse axonal injury. Excluding the surgical management of mass lesions (hemorrhage) and depressed skull fractures, there is little that we as veterinarians can do about the primary injury. However, minimizing the incidence or impact of secondary brain injury is the focus of the emergency medical management of the small animal TBI patient. Secondary brain injury refers to a variety of pathophysiologic processes that culminate in progressive neuronal damage at sites both local to and distant from the primary injury. These include, but are not limited to:

- **Decreased ATP:** Massive depolarization occurs after head trauma. Restoration of electrical gradients is dependent on adequate ATP levels. ATP will be depleted in association with this process. Failure of ATP-dependent membrane pumps can result in increased intracellular calcium (see below) as well as cellular edema and thus increased intracranial pressure (ICP).
- **Decreased Global Oxygen Delivery (DO_2):** Oxygen delivery to any tissue in the body is dependent on blood flow (Cardiac Output [CO]) and oxygen content of the arterial blood (C_aO_2). Cardiac output is equal to the product of stroke volume and heart rate. Stroke volume can be depleted in the trauma patient secondary to blood loss, restricted fluid administration, and the administration of diuretics. C_aO_2 is largely determined by [Hgb] and oxygen saturation. C_aO_2 can be depleted through alterations in blood hemoglobin concentration (hemorrhage) and oxygen saturation (pulmonary contusion, pleural space diseases, etc). Insufficient oxygen delivery to neuronal tissue will accentuate the already depleted ATP levels and predispose to the accumulation of lactic acid through anaerobic glycolysis. Aggressive resuscitation of the trauma patient will minimize the occurrence of secondary brain injury from decreased DO_2 (see below)
- **Excitotoxicity:** Glutamate is an excitatory neurotransmitter. After trauma, glutamate concentrations in the extracellular fluid increase resulting in an increase in intracellular calcium concentration. Elevated intracellular calcium concentrations then result in direct and indirect neuronal cell injury.
- **Other Mediators:** NO, complement, kinin, and coagulation/fibrinolytic processes.
- **Systemic Metabolic Disturbances:** Hypoglycemia will result in a decrease in the amount of substrate for ATP production.
- **Altered Vascular Reactivity (loss of autoregulation):** Autoregulation of blood flow occurs clinically on many levels and is responsible for the maintenance of appropriate blood flow to the brain across a variety of physiologic alterations. Pressure autoregulation refers to the ability of the cerebral vasculature to maintain cerebral blood flow across a variety of blood pressures (between a mean of 50–150 mmHg). Below 50 mmHg, cerebral blood flow falls, and above 150 mmHg, cerebral blood flow increases. After trauma, pressure autoregulation can be lost globally or locally resulting in a linear relationship between mean arterial pressure (MAP) and cerebral blood flow and the possibility that despite a normal MAP, cerebral blood flow may be inadequate. Metabolic/Chemical Autoregulation refers to the ability of the cerebral vasculature to regulate blood flow both locally and globally in response to changing metabolic activity of the neurons. Increased metabolic activity stimulates an increase in blood flow regionally (vasodilation), while decreased metabolic activity causes decreased regional blood flow (vasoconstriction). Carbon dioxide concentration also influences cerebral blood flow through its effect on the vasculature. Increased carbon dioxide levels result in vasodilation and decreased carbon dioxide levels can result in vasoconstriction. TBI can result in alterations in these autoregulatory processes resulting in inappropriate degrees of vasodilation or vasoconstriction with consequential inappropriate alterations in regional or global cerebral blood flow. Inappropriate vasoconstriction may result in decreased oxygen delivery to regional neurons while inappropriate vasodilation may result in increased intracranial pressure (ICP). Severe increases in ICP result in decreased cerebral blood flow (CBF). Decreased CBF results in increased CO_2 locally that is detected at the vasomotor center. The vasomotor center instigates a massive response from the sympathetic nervous system resulting in a dramatic elevation in MAP in an effort to increase cerebral perfusion pressure (CPP).

$$CPP = MAP - ICP$$

Increased MAP is detected at the baroreceptor and will often result in a reflex bradycardia. This reflex is called the ischemic response/Cushing reflex: The ischemic response occurs late and requires an intact vasomotor center to occur. Observation of the ischemic response should prompt the clinician to aggressively treat increased ICP (see below).

- The different mechanisms of secondary brain injury culminate in ongoing cellular injury and increased intracranial pressure.

CLINICAL APPROACH TO THE HEAD TRAUMA PATIENT

The approach to the small animal TBI patient should initially address the three major body systems (cardiovascular, respiratory, and CNS) in an effort to identify and institute treatment for immediately life threatening problems. Treatment for problems identified based on the examination of the cardiovascular and respiratory systems should be instituted immediately such that delivery of oxygen to the brain can be maximized. A rapid history including the time of the trauma, clinical signs immediately after the trauma and progression of those signs, medications administered, and previous pertinent medical history should be sought out soon after presentation.

Clinical manifestations and physical and neurologic examination findings in the small animal patient that has suffered TBI may include an altered level of consciousness, seizures, ataxia, proprioceptive deficits, and various cranial nerve deficits. The veterinarian may observe obvious wounds to the head and/or neck region, episcleral hemorrhage, hyphema, epistaxis, oral trauma (broken teeth, jaw), blood in the ears, and fractures on palpation of the bones of the head. Identification of any of the aforementioned injuries should prompt the clinician to consider the possibility of a significant intracranial injury and further diagnostic options. Immobilization of the TBI patient is important due to the possibility of concurrent spinal injury.

A resurgence of attention is being paid to grading the severity of TBI according to the Modified Glasgow Coma Score (MGCS). The MGCS was developed in 1983 by Shores in an effort to grade the severity of neurologic injury, allow for comparison to that baseline over time, and finally to predict prognosis. The scale was proposed as shown in Table 1.

A score is given in each of the categories above and then the scores are totaled. It has been proposed that a score of 3 to 8 suggests a grave prognosis, 9 to 14 suggests a guarded prognosis, and 15 to 18 suggests a good prognosis.[5] Retrospective evaluation of a series of 38 dogs with head trauma correlated the probability of survival within the first 48 hours with MGCS. A prospective evaluation of 24 dogs with head trauma showed that MGCS predicted length of stay, cost of care, and thus severity of injury but concluded that further studies will be necessary to determine if MGCS is a good predictor of outcome. Future studies will also be necessary to determine if MGCS will be a useful predictor of the necessity for CT scan after head trauma in dogs.

Table 1. Modified Glasgow Coma Scale

	Score
A. Motor Activity	
Normal gait, normal spinal reflexes	6
Hemiparesis, tetraparesis, or decerebrate activity	5
Recumbent, intermittent extensor rigidity	4
Recumbent, constant extensor rigidity	3
Recumbent, constant extensor rigidity with opisthotonus	2
Recumbent, hypotonia of muscles, depressed or absent spinal reflexes	1
B. Brainstem Reflexes	
Normal pupillary light reflexes and oculocephalic reflexes	6
Slow pupillary light reflexes and normal to reduced oculocephalic reflexes	5
Bilateral unresponsive meiosis with normal to reduced oculocephalic reflexes	4
Pinpoint pupils with reduced to absent oculocephalic reflexes	3
Unilateral, unresponsive mydriasis with reduced to absent oculocephalic reflexes	2
Bilateral, unresponsive mydriasis with reduced to absent oculocephalic reflexes	1
C. Level of Consciousness	
Occasional periods of alertness and responsive to environment	6
Depression or delirium, capable of responding but response may be inappropriate	5
Semicomatose, responsive to visual stimuli	4
Semicomatose, responsive to auditory stimuli	3
Semicomatose, responsive only to repeated noxious stimuli	2
Comatose, unresponsive to repeated noxious stimuli	1
MGCS = A+B+C	

Imaging studies (CT or MRI) of the intracranial structures should be considered in any patient with focal neurologic signs, moderate to severe neurologic signs of TBI on presentation, failure of clinical signs to improve within hours of initiation of treatment, or deterioration in clinical signs. Imaging will allow the clinician to rule in or out a significant mass lesion (epidural, subdural, or intraparenchymal hemorrhage) or depressed skull fractures as contributory to the clinical signs. Mass lesions and depressed skull fractures in patients with moderate to severe trauma and static or progressive clinical signs should be approached surgically. Imaging studies will also allow the clinician a better appreciation for the other injuries (contusion, edema) often present in the head trauma patient.

TREATMENT OF THE HEAD TRAUMA PATIENT

The following will discuss the pros, cons, indications, and contraindications for the various treatment options for the veterinary patient with TBI. Until controlled, prospective studies can be performed in clinical small animal patients with naturally occurring TBI, medical treatment recommendations for small animals must be made based on knowledge gained through human medical research as well as experimental models of head trauma in animals. The limitations of cross-species application of these recommendations must also be noted.

- **Fluid Therapy:** Fluid therapy for the dog or cat that has sustained TBI should be directed towards rapid restoration of intravascular volume and support of CPP through support of MAP. Bouts of hypoxemia or hypotension have been implicated as predictors of poor neurologic outcome in human patients that have suffered head trauma. Fluid therapy should never be restricted in the head trauma patient as dehydration will only result in slight decreases in ICP. At the same time, fluid restriction may jeopardize the MAP and thus CPP. Options for fluid resuscitation of the head trauma patient include isotonic crystalloid fluids, hypertonic saline, synthetic colloids, and blood or blood products.

  Isotonic crystalloid solutions (Normosol-R, 0.9% Saline) are reasonable resuscitation fluids for the patient that has sustained TBI. If isotonic crystalloid solutions are chosen for resuscitation, only that volume necessary to restore euvolemia, provide maintenance, and balance out ongoing losses should be administered.

  Hypertonic Saline resuscitation has the advantages of smaller volume resuscitation, rapid restoration of intravascular volume thus improving CPP, improved contractility, and its osmotic effect at the level of the brain thus lowering ICP. Disadvantages include perpetuation of hypernatremia and the pulmonary vagal reflex that can result in bradycardia during administration. There is some evidence that hypertonic saline may disrupt the blood brain barrier and thus nullify some of its beneficial effects. Hypertonic saline may be administered at a dose of 4 mL/kg of a 7.5% solution by slow IV infusion over 10 to 20 minutes. Diligent monitoring of serum sodium concentration is critical after administration especially with concurrent administration of other hypertonics such as mannitol. The effects of hypertonic saline may be short lived, but may be extended by concurrent administration of a synthetic colloid. Concurrent isotonic crystalloid administration for maintenance purposes and provision for ongoing losses will be required.

  Colloid solutions are considered by some to be the resuscitation fluid of choice in the patient that has sustained TBI. Benefits include a smaller volume necessary for resuscitation (when compared to crystalloid solutions), persistence in the vascular system and thus support of CPP, potential for minimizing vascular leakage, and prolonging the intravascular effects of hypertonic solutions. Hetastarch (6%) (5–10 mL/kg IV) is probably the most readily available colloid for resuscitation of the canine patient with TBI. In cats, the bolus (2.5–5 mL/kg) must be given over 20 to 30 minutes.

  Blood products are a very desirable resuscitation fluid in the patient with concurrent injuries resulting in hemorrhage and hypovolemia. Packed red blood cells, fresh whole blood, and fresh frozen plasma are all acceptable options. The use of hemoglobin-based oxygen carriers (HBOCs) in head trauma requires further investigation.

  Endpoints of fluid resuscitation include normalization of lactic acidosis and base-excess, return of normal or slightly increased arterial blood pressure, physical examination parameters consistent with resuscitation (pink mucous membranes, normal capillary refill time, normal heart-rate, strong pulses), and normal urine output.
- **Glucocorticoids:** The question of glucocorticoid usage is always up for debate with regard to utility in the management of TBI. Examination of the literature finds no consistent advantage to the utilization of glucocorticoids in head injured patients and potentially some disadvantages. According to the Brain Trauma Foundation, "The use of glucocorticoids is not recommended for improving outcome or reducing intracranial pressure (ICP) in patients with severe head injury."
- **Mannitol:** Mannitol is a sugar with a strong osmotic effect that has been shown to decrease both ICP and cerebral edema after traumatic brain injury. Mannitol exerts its advantageous effects through intravascular volume expansion, reflex cerebral vasoconstriction (decreased CBV) secondary to decreased blood viscosity, osmotic effects, and possibly through its free-radical scavenging effects. Undesirable effects of mannitol include its diuretic effect that could predispose to decreases in intravascular volume and subsequent decreases in DO_2 to the brain. Free water losses at the kidney may also result in hypernatremia after mannitol therapy. Close monitoring of electrolytes (primarily

sodium) is critical to the management of patients who have received mannitol. Dosage ranges from 0.25–1 g/kg IV. Intermittent bolus therapy may be superior to CRI and may avoid the reverse osmotic shift phenomena in which brain concentrations of mannitol exceed blood concentrations thus perpetuating cerebral edema. As a general guideline, no more than three doses of mannitol should be administered within a 24-hour period.

- **Hyperventilation in Head Trauma:** Hyperventilation (decreased P_aCO_2) results in decreased ICP through vasoconstriction of cerebral vasculature. Vasoconstriction, however, will result in decreased cerebral blood flow and thus decreased oxygen delivery to neurons (cerebral ischemia). Prolonged hyperventilation has been associated with inferior neurologic outcomes in people with severe injury when compared to those in which hyperventilation was avoided. Hyperventilation is only recommended as an emergency and transient effort to lower ICP. TBI patients undergoing anesthesia for diagnostic or therapeutic procedures should have P_aCO_2 kept in the 35 mmHg range. The advantage of positive pressure ventilatory support is that both oxygenation and ventilation can be controlled and episodes of desaturation of hemoglobin can be minimized.
- **Elevation of the Head:** Placing the patient on a board such that the head is approximately 15 to 20 degrees above the pelvis may improve cerebral venous drainage. Excessive elevation may decrease CPP and elevation of just the head may result in compression of the jugular veins and thus decreased venous drainage (and secondarily increased ICP). Jugular vein phlebotomy and catheterization is avoided for similar purposes (decreased venous drainage).
- **Oxygen Therapy:** Oxygen therapy should me administered to maximize oxygen saturation of hemoglobin as measured by pulse oximetry at the bedside. When providing oxygen to the head trauma patient, we should strive to make oxygen saturation approach 99%. Oxygen can be administered by cage, mask, hood, nasal cannulae, or transtracheal delivery methods. Those methods that cause coughing or sneezing should be avoided if at all possible as these effects may transiently increase ICP. If oxygenation cannot be maintained without F_iO_2 > 0.6 (60%), positive pressure ventilation is indicated.
- **Seizure Prophylaxis:** The incidence of early and late post-traumatic seizures in the veterinary head trauma patient is currently unknown. At the present time, in human medicine, routine seizure prophylaxis for late onset seizures is not a standard recommendation. Anticonvulsants are recommended for early posttraumatic seizures.[10] In veterinary medicine, benzodiazepines (for the actively seizing patient) and barbiturates (phenobarbital) are the most readily available drugs for this purpose. The author utilizes phenobarbital for seizure prophylaxis in patients that have demonstrated seizures in the early post-traumatic period. Treatment is continued for a minimum of 2 months.
- **Sedation/anesthesia in the small animal with TBI:** Cardiovascular and respiratory sparing sedation protocols are optimal in TBI (oxybarbiturates, opioid/benzodiazepine combinations). $ETCO_2$ and oxygen saturation (SpO_2) should be monitored to avoid episodes of hypoventilation and hypoxemia. Blood pressure should be monitored closely and hypotension should be avoided. Ketamine is not recommended due to increases in ICP that result after administration.

MONITORING THE TBI PATIENT

Monitoring of the veterinary TBI patient should focus on the three major body systems. Blood pressure (oscillometric, Doppler, or direct arterial blood pressure) should be monitored every 1 to 2 hours or more frequently as deemed necessary. Systolic blood pressure should ALWAYS be greater than 120 mmHg recognizing that in the absence of pressure autoregulation, cerebral blood flow may be reduced even at this pressure. A goal of MAP 80 to 120 mmHg is reasonable. ECG monitoring on a continuous basis is excellent for assessment of heart rate and rhythm. Bradycardia may be a sign of severe increases in ICP. Continuous pulse oximetry allows the veterinarian to monitor for bouts of arterial desaturation (a common cause of secondary brain injury). SpO_2 should approach 99%. Arterial blood gas analysis and/or end-tidal capnography will allow the clinician to assess P_aCO_2 levels and possibly avoid bouts of hypoventilation (>40 mmHg). Much of the monitoring equipment available today has functions for preset alarms. Utilization of these alarms to sound upon desaturation, bradycardia, hypotension, etc. is useful. If mannitol or hypertonic saline are being utilized, frequent assessment of electrolytes (at least twice daily) is critical to avoid hypernatremia or a host of other electrolyte abnormalities. Electrolytes, acid/base status, and blood glucose should always be assessed at least once daily in the critically ill patient and fluid therapy adjusted to maintain electrolytes within normal limits. Normalization of blood glucose may be beneficial to the patient that has suffered head trauma. Measurement of urine output via urethral catheterization will facilitate calculation of fluid ins-and-outs such that fluid therapy can be tailored to help maintain euvolemia and hydration. Frequent neurologic examinations focused on MGCS can help identify both progressive intracranial conditions and clinical improvement. Any negative changes in physiologic parameters or physical exam parameters should instigate rapid diagnostic and therapeutic responses on the part of the clinician.

CONCLUSION

Traumatic brain injury is a common occurrence in the polytrauma patient. Attention must first be paid to immediately life threatening processes and then directed towards support of major injuries. Thorough physical examination followed by appropriate diagnostic testing and therapeutic strategies will maximize the likelihood of a positive outcome.

FOOTNOTES

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TRANSFUSION MEDICINE FOR THE GENERAL PRACTITIONER

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SELECTING CANINE AND FELINE BLOOD DONORS BASED ON TYPE

Dog Erythrocyte Antigens (DEA) are glycolipids and glycoproteins on the surface of the red blood cell. The presence or absence of these DEA defines the blood type of an individual. Currently, it is believed that greater than 13 DEA exist. Of these, 8 are considered international standards (DEA 1.1, 1.2, 3, 4, 5, 6, 7, 8) and antisera (for typing) exist to six of them (DEA 1.1, 1.2, 3, 4, 5, 7). It is also possible to type for DEA 1.3. The blood type of the "universal" canine blood donor varies dramatically based on individual theory, laboratory investigation, clinical experience, or a combination of these. There are two "poles" of the universal donor typing debate.

At one end of the spectrum, is the philosophy that the universal donor is one that is positive for DEA 4 (as are 98% of the population) and negative for all other DEA for which antisera (for typing) exist and negative for all anti-DEA antibody (Ab). This approach to selecting the "universal" canine donor is most likely to minimize the likelihood of an acute hemolytic transfusion reaction, maximize the lifespan of the transfused blood and make future cross match most likely to be compatible with the recipient.

At the other end of the spectrum is the theory that because DEA 1.1 is the DEA clinically implicated most often as a cause of acute transfusion reaction in previously sensitized dogs, this is the only DEA that we must routinely type for. This approach to selecting the "universal" canine blood donor will maximize the size of the donor pool.

Practical Recommendations for Selecting Canine Donors Based on Type

- Type potential canine donor dogs with card test as DEA 1.1(+) or 1.1(-)
- Only consider using DEA 1.1(-) donors OR use DEA 1.1(+) donors for DEA 1.1(+) recipients and DEA 1.1(-) donors for DEA 1.1(-) or 1.1(+) recipients
- Proceed to further screening (see below)

Selection of feline blood donors based on blood type is much more straightforward than the canine system. Cats have three possible blood types: A, B, and AB. In the Northeastern United States, Type A cats account for approximately 99.7% of the feline population while Type B accounts for approximately 0.3% of the population. Type AB is extremely rare. Twenty to 45% of Exotic and British Shorthair Cats, Cornish and Devon Rex and 11-20% of Abyssinian, Barman, Persian, Somali, Sphinx, and Scottish Fold are type B. Unlike dogs, cats possess strong naturally occurring antibody to the opposite blood type. Consequently, inappropriate transfusion of Type A blood into a Type B cat will result in death. Transfusion of Type B blood into a Type A cat will result in an acute hemolytic transfusion reaction, but will probably not be fatal. To further illustrate the importance of feline blood typing, we can examine the phenomena of neonatal isoerythrolysis. Type A kittens born to a Type B queen will receive strong anti-A antibody in the colostrum resulting in life threatening hemolysis. Feline blood typing is available through commercial laboratories or via an available card test.[a,b] More recently, a new feline erythrocyte antigen designated *Mik* has been identified to which naturally occurring antibody also appears to exist in *Mik* (-) cats. *Mik* (-) cats may develop acute hemolytic transfusion reactions after being transfused with *Mik* (+) but AB compatible blood. It appears that a majority of cats are *Mik* (+).

Practical Recommendations for Selecting Feline Donors Based on Type

- Type potential feline donors as Type A or B. Try to identify a donor of each type to be available for donation.
- Only consider using Type A blood for Type A cats and only consider using Type B blood for Type B cats
- When transfusion is urgent, transfuse with type specific blood.
- When transfusion is elective, crossmatch to identify
- Proceed to further screening (see below)

SELECTING CANINE AND FELINE BLOOD DONORS (FACTORS OTHER THAN TYPE)

Numerous selection factors other than blood type are critical to ensuring the safety of canine and feline blood transfusions. Screening for these factors can be somewhat time-consuming and costly; however, if it prevents morbidity or mortality to the donor or the recipient, then the increased effort is well worth the added time and expense.

After we have identified dogs with suitable blood type for donation (see above), in the Northeastern United States, we must screen for infectious diseases[6] including *Ehrlichia canis* (IFA), *Babesia canis* and *B. gibsonii* (PCR), *Mycoplasma haemocanis* (*Haemobartonella* sp) (PCR), *Ehrlichia* genus (PCR), *Leishmania* (IFA), and heartworm disease (*Dirofilaria immitis*) (Ag). Appropriate donors should have negative antibody titers to *Ehrlichia canis* and *Leishmania* spp, negative *Babesia* spp PCR, negative *Mycoplasma haemocanis* PCR, and negative *Ehrlichia* genus PCR, as well as a negative heartworm antigen test (concurrently receiving preventative).[c] Recent concern regarding the blood-borne transmission of leishmaniasis to a number of patients at a veterinary teaching hospital has prompted the recommendation to avoid using Foxhounds for donation and to consider random testing of the general donor population. Additional infectious disease testing that may be recommended includes *Brucella canis* (RAST), *Bartonella vinsonii* (IFA), and *Trypanosoma* spp (IFA). In addition to being free from infectious disease, potential donors should be less than 8 years of age, have a normal complete blood count (CBC), serum biochemical profile, and urinalysis, no previous medical problems, a body weight greater than 40 pounds, no concurrent medications, an appropriate vaccination history, no previous transfusion history, and a personality that will allow for sustained restraint for blood collection. The author currently also evaluates donors for von Willebrand Factor levels. All screening with the exception of blood type and von Willebrand factor level should be repeated on an annual basis.

Additional screening (beyond blood type) for feline blood donors in the Northeastern United States is similar to that utilized in dogs. Infectious disease screening should evaluate potential donors for FeLV (Ag), FIV (Ab), *Mycoplasma haemofelis* and *haemominutum* (PCR), and *Bartonella* spp (PCR). Due to the behavior of FeLV and the immune response to it, the author currently screens cats initially for FeLV using an antigen test, followed by a second test after 3 months of complete isolation from other cats. Suitable donors should be FeLV negative, FIV negative, and have negative PCR for *Mycoplasma* spp. Donor cats should weigh greater than 10 lbs, have normal CBC, serum biochemical profile, and urinalysis, no previous medical problems, no current medications, a good vaccination record, no previous transfusions, and a personality conducive to phlebotomy. Many cats require sedation for blood donation purposes. Regarding environment, donor cats must not have any contact with other unscreened cats, must NEVER go outside, must NEVER have contact with screened cats that go outside, and must be re-screened on a yearly basis. Generally, it is most convenient for donor cats to live in the clinic/hospital where their environment can be well controlled (avoiding other cats). Finally, due to the significant incidence of occult cardiomyopathy in the feline population, the author recommends echocardiographic assessment of donor cats annually as a "donor-safety" factor.

COLLECTION OF BLOOD FOR TRANSFUSION

Prior to blood collection, all canine and feline donors should be weighed, examined, and have a small blood sample drawn for PCV or Hgb determination. If sedation is necessary, the author routinely uses an opioid in dogs (hydromorphone[d] or butorphanol[e]) and ketamine/ midazolam IV or isoflurane[f] by mask in cats.

The area over the jugular vein should be clipped and a surgical preparation performed. For dogs, we routinely use a commercially available closed collection system containing CPDA-1 anticoagulant.[g] CPDA-1 consists of citrate for anticoagulation and phosphate, dextrose, and adenine as precursors for ATP production. Collection in cats is generally performed using an open system consisting of syringe(s) with a 1 mL CPDA-1 per 9 mL of blood and a 19-gauge butterfly catheter. Risks of bacterial contamination using an open system are significantly greater than those with a closed system. From 400 to 450 mL of whole blood may be collected from dogs and 40 to 50 mL of whole blood may be collected from cats. On rare occasion, cats and dogs may show signs of hypovolemia after donation requiring rapid intravascular volume expansion with IV fluids. If this happens, donation protocol may need to be adjusted. Whole blood should be used immediately if an open collection system was used. To retain clotting factor function, whole blood should be used or processed into components within 8 hours of donation. Whole blood and packed red blood cells collected into CPDA-1 from a closed collection system can be stored in a strictly temperature controlled refrigerator at 4°C for up to 35 days with the addition of additive solutions[h] to improve RBC viability. The blood bags should be turned daily.

BLOOD PRODUCT ADMINISTRATION:

Most transfusions in veterinary medicine are performed electively; however, in emergency situations like hemorrhagic shock, blood and blood products can be administered as rapidly as is necessary (using a pressure delivery system). Blood and blood products should ALWAYS be delivered via a commercially available 170 µm blood filter.[i] A filter with low dead space is best used in cats and small dogs receiving less than 60 mL of blood or blood product.[j] Filtration of the blood will eliminate blood clots and other large particles that could cause embolic disease in the recipient. Elective transfusion of whole blood or packed red blood cells should begin slowly (1–3 mL over 5 min in cats and 0.25 mL/kg over the first 30 min in dogs) while monitoring for signs of transfusion reaction (see below). If no reaction is noted, the transfusion may be delivered over 1 to 4 hours while intermittently evaluating for any evidence of a transfusion reaction. Recipients with underlying heart disease or other conditions that may predispose to hypervolemia should receive their transfusion slowly to avoid volume overload. Whole blood or blood products should NEVER be infused over a period of time longer than 4 hours due to the risk of bacterial proliferation within the product.

TRANSFUSION REACTIONS

Acute immunologic transfusion reaction may occur when antibodies to donor RBCs are present in the recipient plasma. An example would be the administration of Type A blood to a type B cat (you will remember that all type B cats have potent anti-A antibody). In this clinical situation, the donated cells would be rapidly destroyed in 1 to 2 hours and the recipient would likely die. A similar situation would occur if a DEA 1.1 negative dog is transfused twice (more than 3 to 5 days apart) with DEA 1.1 (+) blood. Antibody to DEA 1.1 in the plasma of the recipient would cause the rapid hemolysis of the transfused RBCs. Other less severe signs of acute immunologic transfusion reactions include fever and urticaria. Life-threatening acute immunologic transfusion reactions can be avoided in most cases by the administration of type specific blood and performing major and minor cross match when indicated. Examples of acute non-immunologic transfusion reactions may include air embolism, blood clot embolism, hypocalcemia because of citrate (anticoagulant used in blood collection) toxicity, and bacterial contamination of the product, causing septicemia in the recipient. Delayed immunologic transfusion reactions result from development of antibody that could shorten transfused RBC lifespan. Delayed non-immunologic transfusion reactions could result from the transfusion of blood contaminated with organisms like FeLV or FIV. Delayed non-immunologic reactions can be prevented through appropriate donor screening.

FOOTNOTES

a. Midwest Animal Blood Services Inc. 4983 Bird Dr. Stockbridge, MI 49285.
b. DMS Laboratories, Inc. 2 Darts Mill Road, Flemington, NJ 08822.
c. Available through: Michigan State University Animal Health Diagnostic Laboratory, East Lansing, MI 48824.
d. Hydromorphone HCl Inj. USP. Abbott Laboratories, North Chicago, IL
e. Butorphanol tartrate, Forte Dodge Animal Health
f. Isoflurane USP. Abbott Laboratories, North Chicago, IL
g. Anticoagulant Citrate Phosphate Dextrose Adenine Solution, USP (CPDA-1) Blood Pack Unit. Baxter Healthcare Corp. Fenwal Division, Deerfield, IL 60015.
h. Adsol Red cell Preservation Solution. Baxter Healthcare Corp. Fenwal Division, Deerfield, IL 60015.
i. Blood Set. Abbott Laboratories, North Chicago, IL 60064
j. Hemo-Nate Filter, Gesco International, San Antonio, TX.

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PLACEMENT OF CENTRAL VENOUS CATHETERS: SELDINGER TECHNIQUE

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Vascular access serves as the lifeline to critically ill small animal patients, allowing for delivery of life-saving fluids, blood products, and drugs while simultaneously guiding the resuscitation effort by providing data on arterial and venous pressures.

USES AND INDICATIONS

By definition, the tip of a central venous catheter (CVC) terminates in the cranial or caudal vena cava. Most CVCs are placed in the cranial vena cava via the jugular vein; however, peripherally inserted central catheters (PICCs) may be placed into the central circulation via a peripheral vein. Central venous catheters have many advantages over the more widely used over-the-needle peripheral venous catheters, including the ability to monitor CVP; infuse hyperosmolar or irritant solutions, such as total parenteral nutrition; and reliably and atraumatically retrieve diagnostic blood samples, as is often necessary in critically ill or diabetic patients.

To monitor CVP, the tip of the CVC should terminate in the thoracic vena cava of dogs and the thoracic or abdominal vena cava of cats. Many CVCs have multiple lumens, allowing delivery of several incompatible solutions concurrently or facilitating monitoring of CVP while several types of fluids are being administered. The author considers the multilumen CVC a key tool that facilitates both monitoring and management of critically ill dogs and cats.

CONTRAINDICATIONS AND PRECAUTIONS

General contraindications to placement of a CVC via the jugular, maxillary, or femoral vein include presence of a significant hemostatic abnormality, such as severe thrombocytopenia (<20,000/μL); known severe thrombocytopathia; coagulopathy; or overt bleeding tendencies. They are also contraindicated in patients with disease processes suspected to be associated with hypercoagulable states, such as immune-mediated hemolytic anemia or protein-losing nephropathy, because of concerns about cranial vena cava thrombosis and pulmonary thromboembolism. A CVC placed in the jugular or maxillary veins are also contraindicated in patients with traumatic brain injury because of the potential decrease in cerebral venous drainage that may occur during manipulation of the veins of the neck. Most CVCs tend to be long in length and relatively narrow in diameter, making rapid infusion of large amounts of fluid or blood products difficult.

EQUIPMENT

Central venous catheters come in many varieties, including over-the-needle catheters, through-the-needle catheters, and those placed using the Seldinger technique. Over-the-needle catheters tend to be stiff and prone to kinking when used as CVCs, whereas through-the-needle catheters are usually the single-lumen variety, which create a vascular defect slightly larger than the catheter itself. Many through-the-needle catheters are difficult to secure. The Seldinger technique facilitates cannulation of a vascular structure using a small-gauge catheter or needle, allowing introduction of a flexible guidewire and subsequently a catheter. It has also been used to catheterize other vascular structures and the peritoneal, pleural, and pericardial cavities.

CATHETER SELECTION AND PREPARATION FOR JUGULAR VEIN PLACEMENT

The length should be such that the tip of the catheter lies within the thoracic vena cava at approximately the level of the 2nd rib space. Measuring the distance between the middle of the jugular vein to the 2nd rib space helps in selecting a catheter of appropriate length. The author generally chooses 4-French catheters for very small dogs and cats (< 7 lb), 5.5-French catheters for animals between 7 and 25 pounds, and 7-French catheters for animals heavier than 25 pounds. All lumens of the CVC, and the over-the-needle catheter or introduction needle, should be filled with heparinized 0.9% saline (1 U/mL).

HOW TO PLACE A CENTRAL VENOUS CATHETER (SELDINGER TECHNIQUE)

Note: The following step-by-step procedure discusses placement of a two-lumen, 7-French, 20-cm CVC via the right jugular vein in a dog. In the following series of images, the patient is always positioned in left lateral recumbency and the head is always to the right of the image.

1. Position patient in lateral recumbency and clip from mid-mandible to second sternebra and dorsal midline to the opposite jugular vein (Figure 1). To assess appropriate field preparation, be sure that no hair from the unclipped area can be folded within 5 cm of the proposed insertion site. Prepare the clipped area using alternating chlorhexidine-based scrub solution and alcohol as for surgery. Use sterile gloves during catheter placement. Use of barrier gown and surgical mask further minimizes risk for contamination.

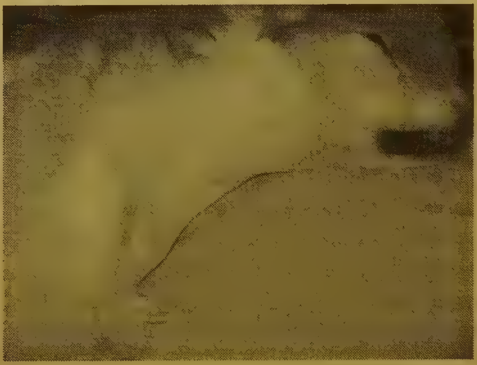

Figure 1.

2. The jugular vein lies between the caudal ramus of the mandible (identified by finger in image) and the thoracic inlet. Place an impermeable drape with a fenestration approximately 3 to 5 cm in diameter over the jugular vein, one third of the distance between the caudal ramus of the mandible and the thoracic inlet (Figure 2).

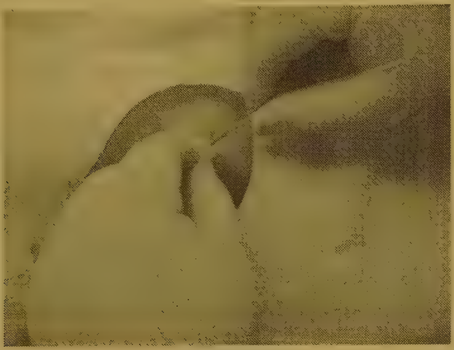

Figure 2.

3. An assistant should occlude the jugular vein at the thoracic inlet to identify its course. The assistant then releases pressure on the jugular vein, so you can tent the skin over the jugular vein and make a 3- to 4-mm incision in the skin using a No. 11 scalpel blade. Point the cutting edge of the blade away from the patient to minimize the risk for injuring underlying vasculature. This small defect eliminates tissue drag and is known as the percutaneous facilitative approach. This step is a variation on the original Seldinger technique, in which the skin incision is made after step 6 (Figure 3).

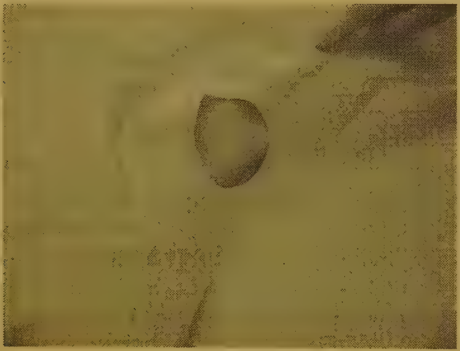

Figure 3.

4. Reocclude the jugular vein at the thoracic inlet and place an over-the-needle catheter (see Figure 5) or thin-walled introducer needle (see Figure 4) into the jugular vein. Most CVC kits contain both an over-the-needle catheter and an introducer needle of appropriate size to accommodate the J-tipped spring guidewire. Attach a syringe filled with heparinized 0.9% saline to the end of the introducer needle or over-the-needle catheter to minimize the risk for air embolus. Intermittent aspiration of this syringe during placement will signify that the jugular vein has been penetrated when a flash of blood is seen in the hub of the needle.

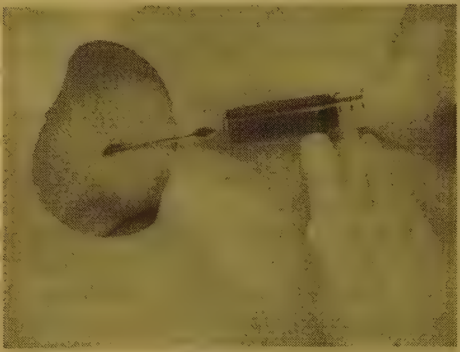

Figure 4.

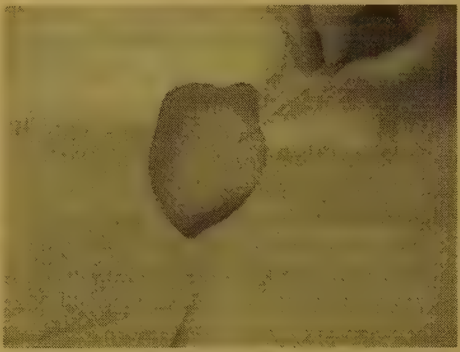

Figure 5.

5. Insert the J-tipped spring guidewire (Figure 6) into the introducer needle or over-the-needle catheter (Figure 7). When the wire passes out of the lumen of the introducer needle or over-the-needle catheter and into the jugular vein, the J-tip will activate, minimizing risk to the vasculature or the heart if the wire comes into contact with it. Note the length of the wire and be sure to advance it only to the level of the cranial vena cava (approximately the 2nd rib space).

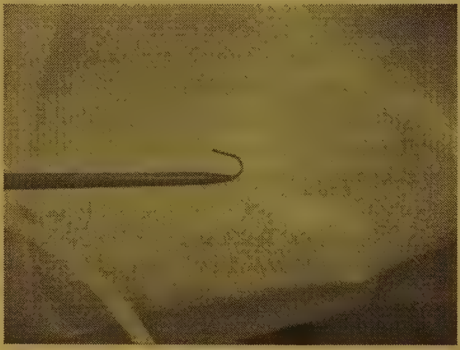

Figure 6.

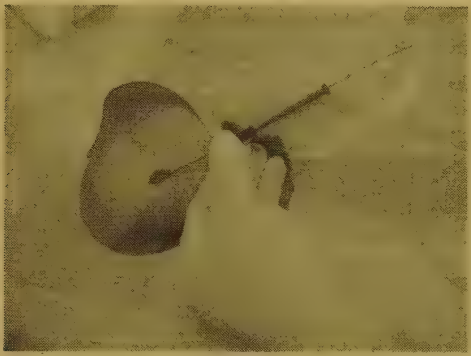

Figure 7.

6. Remove the introducer needle or over-the-needle catheter over the J-tipped spring guidewire. At this stage, only the J-tipped spring guidewire is left in the vessel (Figure 8).

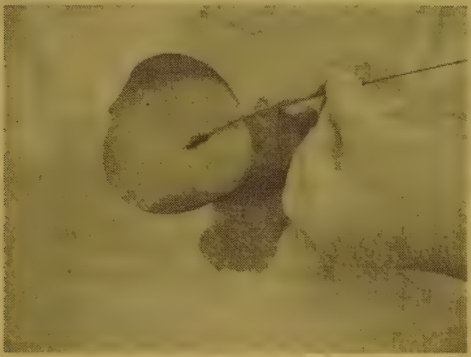

Figure 8.

7. Insert the vessel dilator (see Figure 9) over the J-tipped spring guidewire and into the jugular vein. (see Figure 10) The dilator creates a larger defect in the subcutaneous tissues, allowing the catheter to enter smoothly. Remove the dilator. At this stage, again only the J-tipped spring guidewire should be left in the vessel (as seen in Step 8). Some bleeding may be noted at this time. Apply mild direct pressure at the insertion site to mitigate hematoma formation.

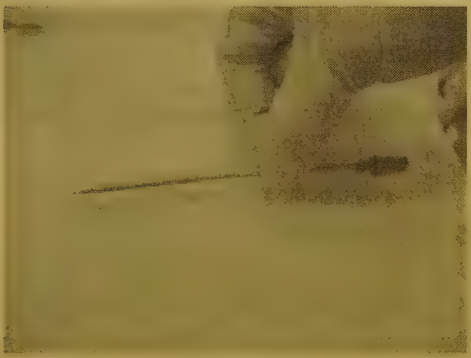

Figure 9

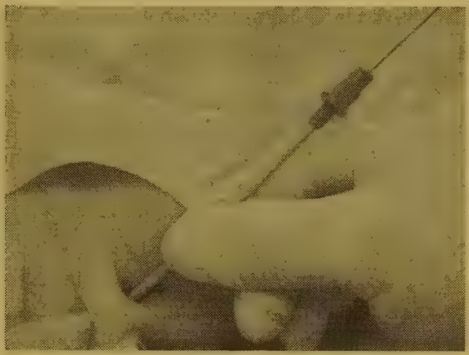

Figure 10.

8. Advance the catheter filled with heparinized 0.9% saline (see Figure 11) over the J-tipped spring guidewire (see Figure 12).

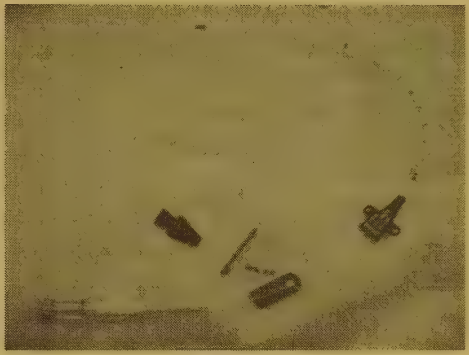

Figure 11.

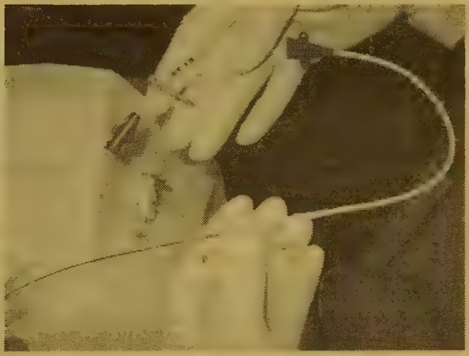

Figure 12.

9. Grasp the end of the J-tipped spring guidewire, which prevents loss of the wire within the patient, and then advance the catheter into the jugular vein. See Figure 13.

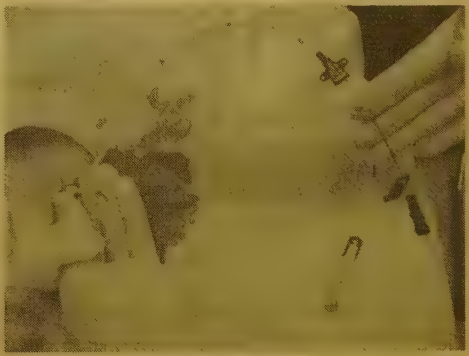

Figure 13.

10. Remove the J-tipped spring guidewire from the catheter, leaving the catheter within the jugular vein (Figure 14).

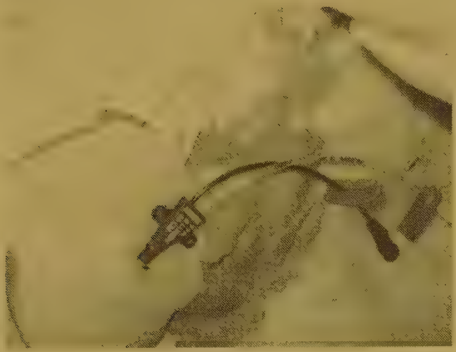

Figure 14.

11. Suture the catheter in place at three anchor points. The "collar" of the catheter should be sutured in line with the jugular vein (Figure 15).

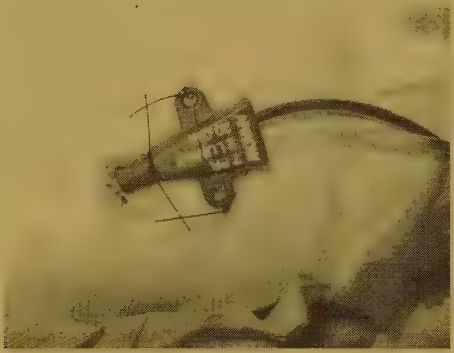

Figure 15.

12. Apply a sterile dressing to the insertion site. Evaluate the dressing and the site daily for redness, swelling, or discharge, and change the dressing daily. Most CVCs can remain in place for up to 1 to 2 weeks as long as no indications for removal exist (eg, redness, swelling, or discharge at the insertion site; cessation of ability to reliably sample from the catheter; jugular vein thrombosis) (Figure 16).

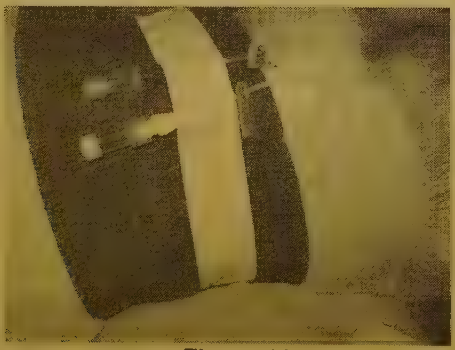

Figure 16.

13. Thoracic radiography may be used to assess the location of the tip of the catheter. (Note: This image is not from the same patient as in previous images but illustrates proper site of placement) (Figure 17).

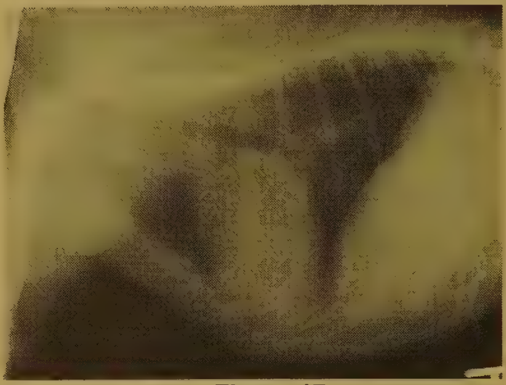

Figure 17.

If a fever or other signs of infection of unexplained origin develop, the catheter should be considered as a likely cause and removed and cultured.

WHAT YOU WILL NEED

- Materials to create a sterile field (clippers, antiseptic preparation solution)
- Drape (usually included with central venous catheter kit)
- Central venous catheter kit (most kits include all necessary materials for placement) (Arrow International; Reading, PA)
- Sterile gloves
- Barrier gown, towel, mask
- Heparinized 0.9% saline solution (1 U/mL)
- Bandages

PROCEDURE PEARLS

- The CVC allows the clinician to measure CVP, to infuse hyperosmolar or irritant solutions (such as total parenteral nutrition), and to reliably and atraumatically retrieve blood samples.
- The tip of the CVC placed for monitoring CVP should terminate in the thoracic vena cava of dogs and the thoracic or abdominal vena cava of cats.
- General contraindications to the placement of a CVC via the jugular, maxillary, or femoral vein include presence of a significant hemostatic abnormality.
- The multilumen CVC is a key tool that facilitates both monitoring and management of critically ill dogs and cats.

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EVERY CLINIC IS AN EMERGENCY CLINIC: RAPID ASSESSMENT — "THE FIRST 15 MINUTES"

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Whether we like it or not, emergencies are a way of life for any practicing veterinarian. A client in their car racing for help is not going to understand "appointment only" or "practice limited to..." The client with an emergency will only understand "Veterinarian" and recognize the practice as a likely place to find help. Regardless of equipment, veterinarians, and there staff need to feel comfortable providing assistance for the emergency patient. This article focuses on basic triage procedures and skills needed in the first minutes of a patient's arrival to save the patients that have a chance at survival.

TRIAGE

The receptionist and veterinary technicians are the front line in any practice. As the first people a client speaks to or meets, they have the responsibility of quickly identifying life-threatening problems. If problems are severe the technical staff may have to initiate resuscitation while calling in the veterinarian.

Triage is a term describing the prioritizing of cases based on their need for emergency care. In busy practice it may mean juggling several critical patients simultaneously. Nursing care of the critically ill or injured animal is challenging due to the dynamic and often severe nature of the underlying diseases or injuries. Careful monitoring of clinical parameters is vital to the assessment and treatment of the patient. With focused attention to detail, deterioration of the patient's condition may be recognized early, allowing for administration of treatment and nursing care that ultimately reduces morbidity and mortality.

Veterinary technicians have the closest and most continuous contact with patients and therefore have the opportunity to recognize subtle changes. While sophisticated monitoring and treatment equipment is becoming increasingly available to veterinary practices, much can be accomplished by using one's senses, common sense and simple equipment.

TELEPHONE TRIAGE

When owners suspect a problem with their pets, their first impulse is usually to call your hospital for advice. When they call, they are concerned and are looking to you for suggestions. If the animal is showing ANY abnormal symptoms, the owner should be instructed to bring the animal to the hospital. It is impossible to completely triage a patient over the phone. Owners may be hoping you will tell them it is OK not to come in. For simple problems, this may be true, but for other problems, not recommending a hospital visit could be a big mistake.

Staff must cautious when recommending any treatment without seeing the animal. Any animal that is obtunded, depressed, seizing needs to be seen immediately. If your hospital is closing, they should be instructed to seek emergency care as recommended by your hospital (an on-call veterinarian or emergency center).

EMERGENCY ASSESSMENT

Any antidotal treatment is useless if vital organ function is lost. Regardless of the problem, an initial assessment must be made of cardiopulmonary function and appropriate actions must be taken early to treat any problems identified. Using an "ABC" approach to any sick animal will keep the emergency team focused on life-threatening problems:

Airway

Be sure the animal has a patent airway. A quick oral exam and finger sweep can remove any obstruction. Visually inspect the larynx for swelling or obstruction. If the animal is obtunded, protect the airway by intubating the animal with a low-pressure cuffed endotracheal tube.

Breathing

Is the animal breathing? Are the breaths of adequate rate and depth? Is oxygen getting from the lungs into the tissues? Observation, auscultation, and examination of the mucous membranes can answer these questions. If the mucous membranes are pale or cyanotic, supplemental oxygen should be provided immediately.

Circulation

Check pulse quality, heart rate and rhythm. If pulses feel week or irregular, and electrocardiogram should be evaluated. Patients in shock should have an intravenous catheter placed, blood samples drawn and fluids ready to administer. If the heart rate is rapid and the pulse quality weak, Shock volumes of crystalloid fluids may need to be given. The volume of fluid required is based on the patient's weight, but you should be prepared to administer a full blood volume each hour if crystalloid solutions are being used. In the dog this will be about 90 mL/kg/hr and for the cat about 44 mL/kg/hr.

A safer, more titrated approach to "shock fluids" would be to divide the total fluid volume into 1/4 volumes [(880 mL divided by 4 = 220 mL) or (900/4 = 225)] and then frequently monitoring, one may determine when it is appropriate to move to the second phase of fluid resuscitation (dehydration phase). If the clinical signs of shock resolve after the first 10 minutes, there is no need to proceed with another bolus of fluid. Move on to the dehydration phase.

One must be cautious about overhydration and hemodilution. Overhydration during the emergency phase is most likely to occur when large volumes are administered to animals with pulmonary contusions, pre-existing pulmonary edema, aspiration pneumonitis, hypoproteinemia, brain injuries, and congestive heart failure.

Reassessment is mandatory. Patients should be continually reevaluated and therapy changed as needed. With aggressive fluid therapy we should expect the heart rate to slow, the pulses to become stronger, and organ perfusion to improve. Clinically the color of the patient's gums should look more normal and the animal should act more alert. Packed cell volume and total solids should be rechecked after 25% to 50% of the total shock volume has been given. If the packed cell volume has dropped below 25% to 30% whole blood, packed red blood cells, or Oxyglobin may be needed. If the total solids drop below 3.5 g/dL or less than 50% of the starting value, consider a colloid such as plasma, hydroxyethyl starch or dextrans.

SUPPORTIVE CARE

Throughout the resuscitation, the patients should be continually monitored for adequate oxygenation and ventilation. Depressed, obtunded, debilitated patients should be turned at regular intervals to prevent pulmonary atelectasis and pressure sores. Closed urine collection system may be employed to assess urine output and prevent soiling. Changes in packed cell volume, and total serum solids may require blood transfusion or other colloid support. Once everything has been done to prevent absorption and hasten elimination of any poison, excellent nursing care will provide the patient time to heal from the toxic insult.

FLUID BALANCE

Frequently check the heart rate, body weight, packed cell volume, total solids, mentation and urine production are essential to determine fluid needs. With patients receiving large fluid volumes, thoracic auscultation should be repeated often, listening for changes associated with pulmonary edema. As technicians spend more time at the patients side, they should be listening to these patients frequently. Assess the response to fluid therapy, make changes if necessary, avoid overhydration and watch for early signs of organ dysfunction.

BLOOD PRESSURE/PERFUSION

Blood pressure can be easily measured indirectly although more invasive direct means are also available. Systolic blood pressure should be maintained above 90 mmHg with the goal being a mean arterial pressure above 70 mmHg. Mean pressures below 60 mmHg can lead to impaired perfusion of vital organs especially the kidneys. The hypotensive patient should be given volume (crystalloids and if indicated, colloids), supplemental oxygen and cardiac support with vasoactive drugs if volume alone can not restore blood pressure. Agents which can be used to improve blood pressure include dopamine, dobutamine and norepinephrine.

HEART RATE AND RHYTHM

Cardiac arrhythmias that compromise cardiac output should be treated appropriately. Supraventricular and ventricular tachycardias can impair ventricular filling and lead to a reduced cardiac output. Ventricular tachycardia with R on T phenomenon can lead to sudden death from ventricular fibrillation and should receive antiarrhythmic therapy immediately. Heart block can lead to functional bradycardia and reduced cardiac output. Because a patient with SIRS is at risk for any number of potentially harmful arrhythmias constant monitoring is important.

TOTAL SOLIDS, ALBUMIN AND ONCOTIC SUPPORT

In a healthy animal albumin provides most of the plasma oncotic pressure. Serum albumin should be monitored and kept above 2.0 g/dL using plasma or whole blood transfusions. Persistent hypoalbuminemia is associated with increased mortality in critically ill animals. When patient size and albumin deficit makes plasma transfusion alone impractical, any one of the synthetic colloidal solutions (hetastarch or dextrans) can bridge the gap and help maintain plasma oncotic pressure.

OXYGENATION AND VENTILATION

Oxygen delivery to the vital tissues is the goal of all resuscitative techniques. Oxygen supplementation (by face mask or an oxygen cage) is a simple emergency drug that can help organ function in critical patients. Since oxygen delivery is a function of arterial oxygen content and cardiac output positive changes in any of these variables can improve oxygen delivery. With fluids and cardioactive drugs supporting vascular volume and blood pressure cardiac output is maintained. When available, arterial blood gas analysis will identify abnormal oxygenation and ventilation. Without arterial blood gas, close attention to mucous membrane color and respiratory rate will give much of same information.

RED BLOOD CELL (HEMOGLOBIN) CONCENTRATION

Another variable in determining arterial oxygen content (and therefore oxygen delivery) is the red blood cell mass. The use of crystalloid fluids, plasma and synthetic colloids during resuscitation and rehydration can significantly hemodilute patients. Although the improvements in cardiac output are important, the use of whole blood or packed red blood cell transfusions should be used to maintain a hematocrit between 27% and 33%.

ACID–BASE BALANCE, GLUCOSE AND ELECTROLYTES

Calcium, sodium, chloride, magnesium, and potassium should be maintained within normal limits. Potassium should be added to maintenance fluids to avoid iatrogenic hypokalemia. Blood glucose should be maintained between 100 and 200 g/day. Drops in blood glucose or levels that are not above normal in the face of added dextrose can be seen in acute sepsis.

RENAL FUNCTION AND MENTATION

Urine output should be monitored continually. Inappropriately low urine output (< 1 mL/kg/hour) may represent acute renal failure and appropriate measures with fluids, diuretics and vasoactive drugs like dopamine should be considered. Monitor BUN and creatinine in these animals as another gauge of renal function.

Mentation is a subjective but important way to gauge neurologic dysfunction. Support of blood glucose, oncotic pressure and serum osmolality will decrease the risk of neurologic injury.

COAGULATION

Disseminated intravascular coagulation (DIC) is a common component of critical illness. Daily screening for evidence of DIC in patients at risk can help the clinician intervene. Examination of a blood smear for decreased platelets and fragmented red blood cells is inexpensive and easy. Activated clotting time is another excellent screening test for the intrinsic and common pathways of coagulation. More specific tests for fibrin degradation products (FDP's) and Antithrombin III (AT III) levels may help guide therapy. Therapy is directed toward decreasing microthrombi (heparin and AT III), providing missing factors (fresh frozen plasma) and improving perfusion.

NUTRITION AND IMMUNE STATUS

Even with appropriate antibiotics, the body must provide basic defenses to destroy and reverse the negative complication of critical illness. Patients with extremely low white blood cell counts may need antibiotics. Monitoring white blood cell count is an important gauge of host defense and response to systemic illness.

Malnutrition results in compromised host defenses. Lack of oral feeding can cause a loss of bowel integrity, leading to bacterial infection of the bloodstream. Enteral feeding using gastrostomy, or jejunostomy tubes may be necessary. Short-term use of nasogastric feeding tubes can also provide important nutrients in animals that will not eat on their own.

PAIN CONTROL AND PATIENT COMFORT

While tachycardia can be a sign of poor oxygen delivery, it is also the result of pain and distress. Animals in constant stress are immunosuppressed. It is vital to the care of the patient that it be made as comfortable as hospitalization will allow. Often patient comfort takes a back seat to convenience in a busy hospital. The appropriate use of analgesics, sedatives, padding, bandage changes and personal contact will have positive effects on the patients overall sense of well-being. A stressed patient requires more oxygen than one resting comfortably.

CONCLUSIONS

The primary veterinary hospital is the most important element to the successful outcome of an emergency case. From the initial phone call, through admission, and throughout hospitalization, the first responders are in the best position to triage vital organ function and patient comfort. With a systematic, ABC, approach to changing patients conditions, life-threatening complications will be identified while there is time to make adjustments in treatment, reverse the process and give the animal time to heal.

FLUID THERAPY

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While the importance of fluid therapy cannot be overstated, the decisions of when, how, how much, and what type of fluid are not always clear. Water is essential to life. Water balance is a delicate interrelationship of forces keeping all fluid compartments saturated without overloading any part of the system. The purpose of this talk is to review the when, how, how much, and what types of fluids to use in a variety of common situations familiar to the small animal practitioner.

HISTORY AND PHYSICAL EXAMINATION

When evaluating fluid needs of a patient, it is useful to know the animal's exact body weight before the onset of illness from the owner or from current medical records. If there are acute decreases in body weight, most of these losses can be attributed to water losses. This will allow a more accurate assessment of dehydration.

A thorough physical examination should be performed; assuming fluid losses are not life threatening. If however, your quick assessment suggests life-threatening complications (abnormal mucous membrane color, abnormal capillary refill times, tachycardia, tachypnea, weak pulse, cool extremities, obvious blood loss, etc.), and then your first goal of fluid therapy will be to save the life of the animal. A thorough physical examination will have to be postponed and shock fluid therapy initiated to stabilize the patient's condition.

Although subjective, physical examination findings are important and should be used when assessing the degree of dehydration. As baseline body weights are not often available, the practitioner must be aware that the assessment of fluid losses is only an estimate; in fact, actual losses frequently are much greater.

Third-space losses involve the accumulation of large fluid volumes in cavities such as the pleural or peritoneal space and intestinal or gastric lumen, or in tissues around fracture or trauma sites. These losses result relative hypovolemia without predictable changes in body weight. Patients with extensive third-space losses are excellent candidates for colloid replacement. With their large molecular size and molecular weight. These compounds stay within the vascular space and help pull water back into circulation.

THE EMERGENCY PHASE

When a patient is hypotensive and has clinical signs of shock, intravascular volume is a priority. If there are no clinical signs of shock, one can proceed to rehydration and fluid maintenance.

The volume of fluid required is loosely based on the patient's weight, but you should be prepared to administer a full blood volume each hour if crystalloid solutions are being used. In the dog this will be about 90 mL/kg/hr. Cats are uniquely sensitive to fluid loading and should receive no more than a plasma volume in an hour (44 mL/kg).

By dividing the total shock fluid volume into 1/4 volumes (22 mL/kg) and close monitoring, one may determine when it is appropriate to move to the second phase of fluid resuscitation (rehydration phase). If the clinical signs of shock resolve after the first 10 minutes, there is no need to proceed with another bolus of fluid. It is now time to proceed to rehydration and maintenance.

One must be cautious about overhydration and hemodilution. Overhydration during the emergency phase is most likely to occur when large volumes are administered to animals with pulmonary contusions, pre-existing pulmonary edema, aspiration pneumonitis, hypoproteinemia, brain injuries, and congestive heart failure.

THE REPLACEMENT PHASE

The volume of fluid administered during the dehydration phase is based on an assessment of fluid needs for (1) returning the patient's status to normal (deficit volume), (2) replacing normal ongoing losses (maintenance volume), and (3) replacing continuing abnormal losses (continuing losses volume).

Maintenance volumes are **normal ongoing losses**. Ongoing losses are divided into **sensible** and **insensible** losses. Sensible losses can be measured and are water losses in the urine and feces. Insensible losses are normal but are not easily quantitated. These water losses occur during panting or sweating. One third of the maintenance volume is made up of the insensible volumes and two thirds, sensible volumes. Traditionally, maintenance volumes have been estimated to be:

60 mL/kg/day

Another formula assumes the basal amount of fluid required is equals basal caloric requirements.

(30 X kg BW) + 70

Because each patient is different, body weight will need to be assessed daily to adjust maintenance fluid volumes so the dehydrated patient gains weight and the hydrated patient maintains body weight. While making sure the patient is getting enough fluid, the clinician and nursing staff need to be aware of signs of fluid excess. Patients with heart or pulmonary problems may lose fluids into the lungs. These patients will become tachypneic, hypoxic, and develop pulmonary crackles.

THE MAINTENANCE PHASE

The last phase of fluid therapy is the maintenance phase. At this point, the patient has received enough fluid to compensate for shock (if necessary) and has had a partial replacement of any deficit volume. Chronologically, this phase begins no sooner than 24 hours after fluids were begun. Objective signals that the patient is ready to be placed in the maintenance phase are an absence of clinical signs of shock or dehydration, and the body weight will have increased by at least the percentage of dehydration already corrected. During the maintenance phase, clinicians will be providing both maintenance volumes and continuing losses volumes.

PARENTERAL FLUID SOLUTIONS

Dextrose Solutions

Because glucose is rapidly metabolized to carbon dioxide and water, the administration of dextrose is physiologically equivalent to administering distilled water. Thus, the main indication for the use of dextrose in water is to provide free water to replace insensible losses or to correct hypernatremia resulting from a water deficit. When added to crystalloid solutions, D5W is also useful in providing an intracellular carbohydrate source in patients with sepsis. Whenever dextrose is given, it is quickly metabolized to water, and the water will redistribute to the intracelleular fluid (ICF) and extracellular fluid (ECF) spaces in volumes commensurate with the water volumes in each compartment.

Dextrose in water should not be used as a maintenance fluid, as it will lead to dilution of all electrolytes. For a patient in shock, D5W is not generally recommended as a replacement fluid; it will be metabolized quickly, and the water generated will be distributed for the most part, to the ICF space and provide minimal expansion of the intravascular space. Administration of D5W subcutaneously may cause electrolyte movement into these tissues and may lead to a decrease in circulating blood volume and shock.

Crystalloid Solutions

"Crystalloids" refers to solutions that are isotonic with plasma and contain sodium as their major osmotically active particle. Crystalloid solutions such as Ringer's lactate or 0.9% sodium chloride (physiologic saline) distribute evenly in the extracellular space when administered intravascularly. Only 25% of the administered crystalloid solution will remain in the intravascular space of the ECF compartment after 1 hour. Equilibrium within the ECF compartments occurs within 20 to 30 minutes after infusion.

Physiologic saline (0.9% NaCl) is often called "normal saline." It contains normal levels of sodium ions (154 mEq/L) but abnormally high levels of chloride ions (154 mEq/L) and is considered an isotonic fluid (310 mOsm/L). "Isotonic" implies that the fluid has the osmolality of the extracellular compartments (290 to 310 mOsm/L). Normal saline is used for acute extracellular volume expansion. It is useful as a replacement fluid in the treatment of hyperkalemia and in the treatment of hyponatremia as seen in hypoadrenocorticism. It should not be used in animals with congestive heart failure, as sodium restriction is normally part of the therapy. It also recommended that physiologic saline not be used in animals with liver disease because of the potential for sodium-overloading resulting from these animal's inability to metabolize aldosterone.

Half-strength saline (0.45% NaCl) is an excellent maintenance fluid. A good choice whenever blood sodium levels begin to climb with long-term crystalloid fluid therapy. It is usually combined with dextrose (2.5%) and potassium chloride. The fluids used for maintenance fluids are meant to replace electrolytes normally lost each day. When insensible and sensible (urine) electrolytes are quantitated, an animal will normally lose 40 to 60 mEq/L of sodium and 15 to 20 mEq/L of potassium. Thus, if you continue to use replacement solutions such as Ringer's, 0.9% saline, Ringer's lactate, Normosol-R, or Ringer's acetate, hypernatremia and increased urinary potassium losses (leading to hypokalemia) may result.

In addition, 0.45% saline is the fluid of choice for animals predisposed to sodium retention; for example, those with congestive heart failure or liver disease. Hypernatremia is uncommon in the dog and cat. When the serum sodium does exceed 156 mEq/L, either D5W or 0.45% NaCl with 2.5% dextrose should be considered as a preferred fluid.

Hypertonic saline (3%, 5%, and 7%) is considered a possible drug for the treatment of shock. The rationale for use of these solutions is that they induce rapid expansion of the ECF fluid compartment, resulting in water movement from the ICF compartment to the ECF compartment. The drawback to this approach is the realization that there is also an expansion of the interstitial space because of the rapid redistribution of crystalloid solutions. Also, the intracellular dehydration that occurs with this approach may adversely affect cellular function. These fluids should only be given intravenously and should be administered slowly to avoid inducing pulmonary edema.

Ringer's solution is a crystalloid replacement fluid. It is more of a balanced replacement solution than LRS, 0.9% NaCl in that there is both calcium (4 mEq/L) and potassium (4 mEq/L) ions, along with sodium (147 mEq/L) and chloride (155 mEq/L). Because of the ionic concentrations, Ringer's solution is often used as a replacement solution in cases of metabolic alkalosis. When the alkalosis is the result of vomiting losses from the upper gastrointestinal tract, Ringer's solution supplemented with potassium chloride will be an excellent fluid.

In diabetes mellitus, Ringer's solution is a good fluid for replacement. Previously, concern was expressed about the sodium and potassium content in Ringer's solution. With the polyuria of diabetes, significant sodium, potassium, and water losses must be replaced. Following ionic replacement, one must consider the influence of sodium on the tonicity of the plasma. Because glucose also increases osmolality, there is the theoretic possibility of cerebral edema. Fortunately, this does not appear to be an important clinical entity in animals.

In diabetes mellitus, the initial plasma potassium levels usually are elevated. This is the result of a metabolic acidosis in diabetes mellitus. Remember, potassium is predominantly an intracellular ion, and when it is elevated on a biochemical profile it is usually are the result of an exchange whereby hydrogen ions move intracellularly and potassium ions move into the plasma. As fluids and insulin are administered, potassium ions move intracellularly, revealing the true hypokalemia seen with diabetes. Thus, potassium chloride usually is required. Before the patient's electrolyte status is determined, the potassium in Ringer's solution will be adequate and will not exacerbate the extracellular hyperkalemia. As insulin is administered, at least 20 mEq of potassium chloride per liter should be added.

Buffered crystalloid solutions include Ringer's lactate and solutions such as Normosol-R that contains both acetate and gluconate. With either of these balanced electrolyte solutions, the buffer will supply bicarbonate. Lactate is metabolized by the liver to form bicarbonate, and muscles and peripheral tissues metabolize acetate to bicarbonate.

Buffered crystalloid solutions are useful in the treatment of mild to moderately severe metabolic acidosis. Importantly, the lactate of lactated Ringer's solution does not contribute to the formation of lactic acid.

Colloid Solutions

Colloid solutions include albumin, fresh-frozen plasma, whole blood and synthetic colloids such as the dextrans (dextran-40 and dextran-70), hetastarch and purified cell-free hemoglobin (Oxyglobin®). They act primarily to expand the plasma volume. The rationale for using colloid solutions is from the maldistribution of extracellular water, with relative expansion of the interstitial space water, in the face of a plasma volume deficiency with traumatic and septic shock. This maldistribution of interstitial space water will predispose the patient to pulmonary edema and acute respiratory distress syndrome.

With colloid solutions such as the dextrans, the molecules are distributed in the ECF compartment, mainly the intravascular space. The particle sizes of the various dextrans affect the duration of their presence within the intravascular space and therefore the duration of volume expansion. Dextran-40 contains particles with molecular weights ranging from 10,000 to 80,000. Dextran-70, and hydroxyethyl starch (Hetastarch) contains particles with a molecular weights of 40,000 to 100,000. The half-life of particles with molecular weights of 14,000 to 18,000 is 15 minutes, whereas particles with molecular weights greater than 55,000 have half-lives of several days. As a general statement, only 20% of dextran-40 and 30% of dextran-70 remain in the circulation for more than 24 hours.

Indications for the dextrans include volume expansion and promotion of peripheral blood flow. Studies have shown dextrans to improve survival and hemodynamic parameters in shock. The resultant volume expansion following the use of dextrans is at the expense of the intracellular water.

Plasma is another colloid solutions and is often underused by veterinarians. It is easy to collect and, when frozen, is considered a stable colloid for 2 to 5 years. Fresh frozen plasma is frozen within 6 hours of collection at –70°C and is stable for 1 year (after one year it can still be used for its colloidal effect as describe for regular plasma. Plasma contains important proteins (albumin and globulins), which are useful in liver failure, hemodilution, and hypoproteinemia. An important use of fresh-frozen plasma is for specific or multiple clotting factor replacement. It is not used for the routine management of acute volume deficits when crystalloid solutions or commercial synthetic colloids work as well. The usual clinical dose of plasma is 5 to 10 mL/kg. Fresh-frozen plasma should be administered within 6 hours of thawing to obtain the maximum amount of clotting proteins. Compatibility should be evaluated when previous transfusions have been performed.

Human albumin is available in 5 and 25% solutions. It is felt that one unit of 25% albumin provides the same amount of albumin as contained in one unit of K9 plasma. When available it may be an economical alternative to massive plasma transfusion in critically hypoproteinemic patients. Because it is a human protein patients may become sensitized to the product. It is recommended that it be clear in the patients record if they receive human albumin and repeated dosing (weeks or months later) been approached with caution.

Whole blood is the colloid administered most commonly by veterinarians. It has the advantages of availability and ease of collection and storage. The most common uses of whole blood are for anemia and severe hemodilution. Although anemic patients may not need the plasma portion, whole blood will continue to be used routinely. As anemia is generally defined as a decrease in red blood cells, the use of packed red blood cells (where the plasma has been removed thereby concentrating the red blood cells) is the most logical means of stretching the usefulness of a unit of whole blood and also of providing needed blood components.

A unit of whole blood contains approximately 450 mL of red blood cells, plasma, white blood cells, and platelets. At the end of 24 hours of storage, very few platelets within the whole blood are hemostatically effective.

Oxyglobin is a purified bovine hemoglobin available to veterinarians. It is currently only approved for use in dogs but has been used in many species where whole blood was unavailable. Through purification, the nephrotoxic effects of free hemoglobin have been eliminated. Oxyglobin is a potent colloid with all the volume-expanding properties of a synthetic colloid and the added benefit of increased oxygen carrying capacity. Oxyglobin can be stored at room temperature for up to 3 years. It requires no cross matching (as there are no red blood cell surface antigens), and may improve hemodynamics by increasing vascular tone in some states of shock. The major disadvantage to Oxyglobin is its short duration of action (24 to 48 hours), the effect of free hemoglobin on some blood chemistry tests, and the increase in afterload that may be seen in euvolemic animals.

USE OF LACTATE MONITORING

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Hyperlactatemia and lactic acidosis are important features of shock. Lactate and lactic acid have been recognized as a cause of acidosis in metabolically active tissues (exercise) and poorly perfused tissues (circulatory shock). Lactate, a metabolite formed during the oxidation of glucose, accumulates in anaerobic tissues. Lactate production enables energy production to continue during anaerobic conditions. By converting excess pyruvate to lactate, the cell regenerates NAD$^+$ for ongoing glycolysis. Hyperlactatemia occurs whenever the rate of lactate production exceeds that of lactate extraction from the blood. When its production exceeds extraction, high circulating levels can accumulate. Patient-side tests of lactate can be useful in assessing a patient's whole body perfusion status. Normal blood lactate is 1.5 to 2.5 mmol/L. A blood lactate concentration in the range of 3 to 5 mmol/L constitutes a mild increase, 5 to 10 mmol/L is a moderate increase, and greater than 10 mmol/L represents a severe elevation. Hyperlactatemia is defined (in people) as a blood lactate concentration of 2 to 5 mmol/L without metabolic acidosis. Lactic acidosis (again a human definition) is a blood lactate concentration $\geq$ 5 mmol/L with an arterial pH below 7.35. Glycolysis often works faster than the oxidation of pyruvate. For this reason hyperlactatemia can occur in conditions which favor glycolysis (sepsis, alkalosis, or during glucose infusions) and during times of tissue hypoxia. Tissue hypoxia occurs when energy requirements outpace aerobic metabolism, as in exercise, circulatory shock, or seizures. Clinically hyperlactatemia is most often due to poor perfusion and inadequate tissue oxygen delivery. Lactate concentration in the blood is a quantitative measure of tissue hypoperfusion and a valuable measure of the severity of systemic oxygen delivery. This makes it useful when trying to assess the response to treatment in critically ill people and animals.

Lactate is either converted into pyruvate or eliminated from the body. The liver clears most of the lactate load with the kidneys also playing a role. The Cori cycle provides a path for these tissues to clear lactate while providing glucose to tissues favoring this energy substrate. The normal elimination half-life of lactate is less than 1 hour but can increase to over 2 hours with disease.

SAMPLE COLLECTION

Patient disposition, blood sampling technique, and sample handling can affect the measurement of plasma lactate. Prolonged venous occlusion and restraint can cause mild elevations in lactate concentration (2.5–3.5 mmol/L). Muscular activity during our around the blood sampling is an important variable, with levels as high as 6 to 7 mmol/L seen in normal dogs which exercise before venipuncture or in those with generalized muscle fasciculations (muscle tremors or seizures). Prolonged vascular stasis (holding off a vein) may artificially increase measured blood lactate. If there will be a delay in testing, blood samples should be held on ice, or separated from red blood cells. If the sample is analyzed within 30 minutes, the values should be fairly consistent. Lactate concentration in blood samples held at room temperature rise about 0.2 mmol/L after 30 minutes. This is thought to be due to glycolytic activity in red blood cells.

MEASURING BLOOD LACTATE

Originally, lactate measurement took a relatively large quantity of blood and the analysis could take over an hour. Today, blood lactate can be measured quickly using microliter samples of whole blood or plasma. Numerous patient-side systems are in use and all use similar enzymatic amperometry methodology to determine lactate concentration. The drive to create a quick, portable, lactate analyzer came not from the critical care/emergency fields, but from sports medicine. Endurance athletes and their trainers looking for objective ways to identify target heart rates knew that lactate levels often determine an athletes ability to go faster and farther. Lactic acid production by skeletal muscles must be balanced by the body's ability to clear the lactate. This lactate threshold becomes an important variable. By developing quick, small blood volume tests, athletes and trainers can precisely determine an athlete's lactate threshold and provide targeted training.

DIAGNOSTIC AND PROGNOSTIC VALUE OF LACTATE MEASUREMENT

As with all objective data, lactate measurement must be interpreted along with other patient care variables. Clinicians would like to just look at a number and gain insight into the patient's ability to deliver oxygen. Ideally it would be great if we could get an idea of prognosis based on that number. Admission lactates that are above normal only indicate that lactate production exceeds lactate clearance. Is the patient active? Did it just come from a walk/run? Did the patient struggle when the sample was obtained? These are important questions as clinicians look to other signs of impaired tissue oxygenation. Equally important, a normal blood lactate just tells the clinician that lactate clearance is keeping up with lactate production. A patient with seriously impaired oxygen delivery (shock) that hasn't exceeded its lactate clearance mechanisms could have a normal blood lactate.

There are some veterinary examples making good use of admission lactate values. A retrospective study of 102 dogs with gastric dilatation volvulus from the University of Pennsylvania showed that in the prediction of gastric necrosis, a plasma lactate greater than 6.0 mmol/L had a specificity of 88% and a positive predictive value of 75% but sensitivity was only 61%. Survival in these dogs was 99% if the plasma lacate was less than 6.0 mmol/L but only 58% if it was greater than 6.0 mmol/L. The same group also looked at plasma lacate in dogs with congestive heart failure from valvular disease and cardiomyopathy. In these cardiac patients, plasma lactate was significantly higher in nonsurvivors. In a prospective study of 16 dogs and cats with bacterial peritonitis and 55 with other causes of abdominal effusion, PLC in abdominal fluid from bacterial peritonitis was significantly higher than in nonbacterial effusions; however, the degree of overlap between groups limited its usefulness in individual animals.

More important than admission lactate is what happens to that lactate as we begin treating our patients. If our interventions result in improved oxygen delivery to tissues and improved renal and hepatic lactate clearance, our patient's lactate should return to normal. However, if our patient's blood lactate climbs in the face of treatment we are losing the battle and more aggressive measures need to be found to reverse the anaerobic conditions affecting our patients.

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ABCs OF ACID–BASE

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Have a new graduate working for you who keeps bugging you to buy a blood gas machine? Not sure what extra information that blood gas might tell you anyway? Intimidated by all those scary, acid–base numbers? Can't remember how to interpret a blood gas to save your life (or your patient's?). With the improvement in emergency medicine and critical care, the use of blood gas analysis has become more prevalent. Devices such as I-STAT® or NOVA® are available as bedside testing, with results available within just minutes. This requires maintenance of the equipment, training for analysis of the data, and the technical skill to obtain the sample. Depending on the number and types of cases that are seen at your practice, along with the commitment of professional personnel to collect the samples and interpret the results, the use of blood gas analysis is extremely useful in the critical care or emergent setting. Not only can blood gas analysis be used to evaluate underlying disease mechanisms, but it may also aid in potential treatment interventions (ie, the decision to use bicarbonate therapy, to utilize positive pressure ventilation, or to treat with oxygen therapy).

BLOOD GAS ANALYSIS

Blood gas analysis is the determination of the pH, partial pressure of oxygen (PO$_2$), and partial pressure of carbon dioxide (PCO$_2$) of blood. Blood gases allow clinicians to evaluate the acidity of the blood, the overall acid–base status, the respiratory and metabolic contributions, and the pulmonary function. The HCO$_3^-$ is a measure of the *metabolic* component, while the PCO$_2$ is a measure of *ventilation* and is the respiratory component of a patient's acid-base status.

One of the first steps to blood gas analysis is looking at the pH. An "acidemia" is defined as a pH below normal ("acidemia" is acidosis of the blood, to be differentiated from an "acidosis" alone), while a pH above the range is an alkalemia. Severe acidemia ($<$ 7.1) is associated with altered enzymatic activity, decreased cardiac output, impaired renal and hepatic blood flow, decreased arterial blood pressure, neurological alterations, and detrimental cardiovascular consequences (ie, decreased cardiac contractility). Acidosis may also shift the oxygen-hemoglobin dissociation curve to the right, result in insulin resistance, and cause hyperkalemia (by transcellular shifting of K$^+$ for H$^+$); therefore, prompt recognition and treatment should occur. Neurologic signs may also be present with alkalemia, although this is less commonly clinically seen.

An acidosis or alkalosis can be characterized by being metabolic or respiratory in origin, and is due to an accumulation of acid or base, respectively. Metabolic acid-base derangements may be the result of numerous disease processes. **Metabolic acidosis** is the #1 disturbance commonly seen in veterinary medicine, and is characterized by decreased plasma HCO$_3^-$ concentrations and decreased pH. It is most commonly seen with these four causes: diabetic ketoacidosis (DKA), toxicities (eg, ethylene glycol, aspirin), renal failure, and lactic acidosis. **Metabolic alkalosis** is due to increased HCO$_3^-$ concentrations and an increased pH and is most commonly seen with pyloric outflow obstruction or loop diuretic administration. Rarer causes for metabolic alkalosis include hypochloremia, penicillin derivatives, and excessive alkalinization therapy with bicarbonate. As for respiratory conditions, alveolar hypoventilation leads to **respiratory acidosis** which is characterized by increased PCO$_2$ (which simplistically, is an "acid"). Alveolar hyperventilation leads to **respiratory alkalosis**, which is characterized by decreased PCO$_2$ levels ("blowing off" acid). These four primary acid–base disorders are **simple disorders**; in other words, the acid-base abnormality is limited to a primary disorder and its expected adaptive response. Mixed acid–base balance may occur when multiple processes are occurring and is most commonly seen with a "normal" pH. A **mixed disorder** is the presence of two or more separate primary acid–base abnormalities in the same patient, and should be suspected when the adaptive response exceeds or falls short of that expected.

1. The lower the pH, the more acidic a fluid is; the higher the pH, the more basic.
2. Increasing the PCO$_2$ lowers the pH and therefore has an acidifying effect on pH.
3. Decreasing the PCO$_2$ increases the pH and has an alkalinizing effect on pH.
4. Increasing the HCO$_3^-$- increases the pH and has an alkalinizing effect on pH.
5. Decreasing the HCO$_3^-$ decreases the pH and has an acidifying effect on pH.

Table 1. Normal Arterial Blood Gas Values

	Dog	Cat
pH	7.35–7.46	7.31–7.46
PCO$_2$ (mmHg)	32–43	26–36
HCO$_3^-$ (mEq/L)	18–26	14–22
BE	+1 to –5	–2 to –8
PaO$_2$	80–105	95–115

(From DiBartola's Fluid Therapy in Small Animal.) Practice, 2000).

Primary Abnormalities

- Metabolic acidosis (– BE, low HCO$_3$)
- Metabolic alkalosis (+ BE, high HCO$_3$)
- Respiratory acidosis (high pCO$_2$)
- Respiratory alkalosis (low pCO$_2$)
- Hypoxia

In general, the steps for interpretation of blood gas analysis should be the following:

1. pH = acidemic vs. alkalemic?
2. Base excess (BE) = truest component of metabolic component
3. pCO_2 = evaluation of respiratory component
4. Compensatory?
5. Hypoxic?
6. Alveolar-arterial (A-a) gradient
7. Do these changes correspond to the clinical picture?

First, determine if the pH is acidemic, alkalemic, or in the normal range. A normal pH with other disturbances (abnormal PCO_2, HCO_3^-, etc.) is suggestive of a *mixed acid-base* or potentially *compensated* disorder. Evaluate your base excess (BE), which is the amount of titratable acid necessary to bring a pH back to normal irrespective of the respiratory component; in other words, BE is your "truest" interpretation of your metabolic component. If this is excessively negative, you have a primary metabolic acidosis. Next, evaluate the metabolic (HCO_3^-) and respiratory (PCO_2) components. Calculate the degree of compensation to see if the body has compensated for its disease process. Finally, evaluate the blood gas result to see if it corresponds to the clinical picture of your patient.

Important diagnostic and treatment information can be ascertained from an arterial (ABG) or venous blood gas (VBG). The primary differences between an ABG and VBG are the ability to evaluate PO_2 (which is only accurate in an ABG), and a 5 to 10 mmHg difference in PCO_2 (with the venous side having a higher $PvCO_2$). For example, a dog with a pH of 7.0, PaO_2 of 60 mmHg, PCO_2 of 26 mmHg, HCO_3^- of 9 mEq/L, and a BE of –18 has an acidemia, a metabolic acidosis, and hypoxemia. Buffer therapy such as sodium bicarbonate and oxygen therapy should be considered while a search for the underlying metabolic condition is initiated. On the other hand, a cat with a pH of 7.23, pvO_2 of 33 mmHg, PCO_2 of 68 mmHg, HCO_3^- of 25 mEq/L, and a BE of +2 has an acidemia with a respiratory acidosis that has not yet compensated. This patient would benefit from positive pressure ventilation; however, because this is a venous sample, one cannot evaluate the severity of hypoxia. Buffer therapy in this case could be potentially harmful, as bicarbonate is converted to water and CO_2 (which must be "blown off") which may worsen the respiratory acidosis.

A pH in the normal range does not necessarily indicate the absence of acidosis or alkalosis, as an abnormal PCO_2 or HCO_3^- may be due to compensatory mechanisms or multiple simultaneous pathologies which "balance" each other. The clinician must therefore be vigilant in reading the entire blood gas. Lastly, many blood gas analyzers have the capability to measure electrolytes and lactate. These values are also imperative in evaluating and understanding the acid-base abnormality or severity of hypoperfusion (lactate).

COMPENSATION

The body will attempt to compensate for the severity of the primary abnormality, but will **never** overcompensate. Remember that a change in the respiratory or metabolic component produces an **opposite** response to the other component to bring pH back to normal. Respiratory compensation via the lungs is extremely rapid and occurs within minutes, while the kidneys compensate more slowly over the course of hours to days. For example, if an animal has a severe metabolic acidosis (ie, acute on chronic renal failure), it should ideally compensate by hyperventilating and "blowing" off this excess acid (pCO_2). One must consider whether enough time has passed for the animal to compensate and that the underlying disease has been stable during this time for compensation.

Metabolic acidosis:	↓ $PaCO_2$ of 0.7 mmHg per 1 mEq/L ↓ HCO_3
Metabolic alkalosis:	↑ $PaCO_2$ of 0.7 mmHg per 1 mEq/L ↑ HCO_3
Respiratory acidosis:	↑ 0.15 to 0.35 mEq/L HCO_3 per 1 mmHg ↑ $PaCO_2$
Respiratory alkalosis:	↓ 0.25 to 0.55 mEq/L HCO_3 per 1 mmHg ↓ $PaCO_2$

Causes for METABOLIC ACIDOSIS

- GI loss of bicarb
  - Diarrhea
  - Vomiting
- Renal loss of bicarb
- Renal hydrogen retention
- IV nutrition
- Dilutional acidosis

Causes for METABOLIC ALKALOSIS

- Lasix administration
- Pyloric outflow obstruction
- Hypochloremia
- Hypokalemia
- Hypermineralocorticism
- Penicillin derivatives
- Contraction alkalosis
- Excessive alkalinization therapy

VENOUS BLOOD GAS ANALYSIS (VBG)

In severely dyspnea patients or in feline patients, the stress of restraint for ABG sampling is contraindicated. Rather, the use of venous blood gas analysis with pulse oximetry interpretation can be used together and is often times as beneficial as ABG results. For the evaluation of acid-base parameters, a venous blood gas is an attractive alternative as it does not require arterial sampling. Venous samples can be interpreted as

Causes for RESPIRATORY ALKALOSIS

- Hypotension
- Fever
- Sepsis
- Excitement
- Pain
- Brain tumor
- PTE
- Early pulmonary parenchymal disease
- Cytokine release in SIRS
- Inappropriate ventilator settings
- Compensation

Causes for RESPIRATORY ACIDOSIS

- Hypoventilation
    - Neuromuscular
    - Medullary dysfunction
        - General anesthesia
        - Intracranial disease
    - Cervical disease
- Airway obstruction
    - Large airway obstruction
        - Laryngeal paralysis
        - Tracheal collapse
    - Small airway obstruction
        - Chronic airway disease
        - Bronchoconstriction
- Thoracic wall problems
    - Open pneumothorax
    - Flail chest
    - Diaphragm compression
    - Pleural space filling disorder
    - Pleural fibrosis
- Pulmonary parenchymal disease (late)
- Inappropriate ventilator settings
- Dead space re-breathing
- Bicarbonate therapy
- Compensation for metabolic acidosis
- Malignant hyperthermia
- Brain tumor

Causes for HYPOXIA

- Decreased FIO_2
- Inadequate O_2 supply
- Hypoventilation
- Ventilation/Perfusion mismatch
- Anatomic shunting
- Diffusion impairment
- Low oxygen delivery
- Low cardiac output

previously described for an arterial sample, with three known exceptions:

- The PCO_2 is approximately 5–10 mmHg higher in the venous vs. the arterial system.
- One cannot assess PO_2 on a venous sample. Only an arterial PO_2 can provide information regarding the oxygenation function of the lungs. However, with pulse oximetry, SpO_2 (oxygen saturation) can be correlated with an oxygen-hemoglobin dissociation curve and the pO_2 can then be deducted. Pulse oximeter + VBG = ABG.
- When peripheral vasoconstriction, severe shock, hypovolemia, or low flow states (ie, saddle thrombus, tourniquet application) occur, a peripheral venous sample may not be accurate. These conditions may result in tissue acidosis which may increase CO_2; technically, ventilation *should* keep pace with delivery of CO_2 from the tissues to the lung. Remember that a mixed or jugular venous sample may better reflect the acid–base status of the patient than one from an artery of an affected limb (as long as the patient is not coagulopathic or thrombocytopenic).

OXYGENATION

The PO_2 is the partial pressure of dissolved oxygen and is directly measured by the blood gas analyzer. In order for oxygen to reach the arterial blood, there must be an adequate source of oxygen delivered (ventilated) to the lungs. In addition, adequate blood flow must pass by functioning alveoli with no impediment to diffusion into the blood. As over 95% of the oxygen in arterial blood is normally carried on hemoglobin, the amount of hemoglobin and its saturation are the main determinants of oxygen content (CaO_2). The oxygen content of blood is the amount of oxygen the blood can deliver to the tissues; any significant decrease can compromise the patient. The dissolved oxygen is in equilibrium with oxyhemoglobin and together makes up the oxygen content of the blood.

The PaO_2 coupled with the $PaCO_2$ provides the clinician with a tool to evaluate lung function. A low PaO_2 is referred to as hypoxemia and signals that there is inadequate oxygen supply (ie, empty O_2 tank on the anesthesia machine), hypoventilation (ie, neuromuscular disease or increased anesthetic depth), venous admixture (ie, ventilation/perfusion mismatch as in pulmonary parenchymal disease such as pneumonia), or a diffusion impairment (ie, neoplastic alveolar infiltration). A patient that is hypoxemic may benefit from oxygen supplementation and/or positive pressure ventilation; subsequent arterial blood gases or pulse oximetry can be used to monitor progression and response to therapy

The measurement of the severity of hypoxemia can be based on several calculations. One commonly used in the ICU setting is the **alveolar-arterial (A-a) gradient**. The use of this formula should be limited to assessment on room air (ie, FiO_2 of 21% or 0.21). The barometric pressure is represented by 760 mmHg, while the water vapor pressure is approximately 47. The respiratory quotient is represented as a denominator of 0.8 (or sometimes as a numerator as 1.2). Based on room air at sea level, this can be simplified to: $PAO_2 = 150 - PaCO_2/0.8$, where normal is 0–15 mmHg. Higher values are suggestive of underlying parenchymal lung disease (from ventilation:perfusion or V:Q mismatch or shunting), and chest radiographs should be done to evaluate for lung disease! Normal A-a values may be seen with hypoventilation (despite abnormal blood gas parameters).

$$PAO_2 = FiO_2\,(760\text{-}47) - PaCO_2/0.8$$

Another popular method for quantifying the lung efficiency is the **PaO_2:FiO_2** ratio. It allows for the comparison of samples obtained *despite different levels of oxygen supplementation*. Normal ratio levels should be 500 (ie, 100:0.21), while <300 is consistent with acute lung injury and < 200 is consistent with acute respiratory distress syndrome. For example, a patient with a PaO_2 of 80 mm Hg on room air has a PaO_2:FiO_2 ratio of 80/0.21 = 381. If this same patient is evaluated later on a FiO_2 of 60% with a measured PaO_2 of 170 mmHg, the PaO_2:FiO_2 ratio is 170/0.60 = 283 and therefore indicates less pulmonary function and a worsening of hypoxemia.

SAMPLING ERRORS

One consideration with arterial blood gases is that sampling errors may occur. For this reason, blood should be collected easily (without delay or excessive negative pressure) and anaerobically (avoiding the presence of air bubbles). It is important to obtain a free-flowing arterial or venous sample, as venous stasis or muscular activity can affect lactate or PCO_2. Samples should also be analyzed immediately; if not, they should be stored in ice water. Otherwise, venous contamination/collection, heparin dilution, delays in analysis, and non-anaerobic collections may affect the PCO_2 or PO_2. In addition, the following situations may also result in "false" results:

- Excess heparin within the syringe: low pH, pCO_2, HCO_3
- Exposure to room air or a large air bubble, which normally has a low $[PCO_2] \rightarrow$ diffusion down the gradient occurs, so the pCO_2 blood sample decreases and pH increases (less acid)
- Exposure to room air or a large air bubble, which normally has a high $[PO_2] \rightarrow$ diffusion down the gradient occurs, so that the pO_2 blood sample increases.
- Standing sample: increased PCO_2, decreased pH (higher temp, more change). Prevent this by putting the sample in an ice bath to prevent ↓ glucose and ↑ lactate due to glycolysis by cells.

CONCLUSION

Blood gas analysis provides valuable information to the emergency critical care clinician, and allows one to evaluate acid–base status, electrolyte function, perfusion (if lactate is available), ventilation, and oxygenation. This may serve to better understand the disease mechanisms, determine therapeutic intervention, and monitor improvement. Arterial or venous blood gas analysis can provide valuable insight into a patient's acid–base and ventilatory status. The use of blood gas analysis should be warranted in emergency and critical care cases, and interpreted with care to aid in improved quality care of these critically ill patients.

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References are available from the author upon request.

MISCONCEPTIONS ABOUT EMERGENCY AND CRITICAL CARE

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With the improvement in emergency and critical care, new modalities or approaches have recently arisen. These updated techniques are based on both veterinary and human scientific research and clinical experience and may refute older modalities. As a result, there are many misconceptions that should be updated and reviewed in our current application to veterinary medicine. With appropriate implementation in the clinical setting, we can help increase survival of our critically ill patients.

Some common misconceptions about emergency and critical care include:

- Do we give steroids in head trauma?
- Should I use steroids in shock?
- What are anti-inflammatory vs. immunosuppressive doses of steroids?
- Dextrose in intravenous (IV) fluids is always warranted in hospitalized animals to help maintain nutrition.
- Septic, shocky cats look just like septic, shocky dogs.
- VPCs should always be treated with lidocaine or procainamide.
- Analgesics should be withheld in critically ill patients because it causes respiratory depression.
- IV fluids: does it matter what bag I grab?

DO WE GIVE STEROIDS IN HEAD TRAUMA?

Recently, the use of steroids in head trauma in both human and veterinary medicine has been widely debated. While there is voluminous research in this topic, there are no experimental or clinical studies demonstrating a *clear* benefit of steroids in head trauma. In one human study, a meta-analysis of randomized controlled trials did not show a beneficial response from steroid therapy. Unfortunately, steroids have been associated with the following deleterious side effects:

- GI bleeding
- Hyperglycemia
- Immunosuppression
- Delayed wound healing
- Perpetuation of a catabolic state

The brain trauma foundation guidelines state that glucocorticoids are "not recommended for improving outcome or reducing intracranial pressure in head-injured patients." The "CRASH" study demonstrated that the overall mortality was statistically higher in those patients who were treated with steroids. In fact, recent studies have shown that human patients with head trauma and hyperglycemia have a *poorer* return to cognitive function than do euglycemic patients.

Why is hyperglycemia dangerous with head trauma or in any patient with brain ischemia (ie, epileptic, brain tumor)? Unfortunately, elevated glucose concentrations provide a substrate for anaerobic metabolism and glycolysis in the brain, worsening brain perfusion via the accumulation of the byproduct, lactic acid. In addition, hyperglycemic is associated with pro-convulsant effects, which is due to increased neuronal excitability. In a veterinary study by Syring et al, 52 dogs and 70 cats with head trauma were compared with 122 age- and species-matched control dogs and cats. In this study, the severity of head trauma was classified as mild, moderate, or severe, and blood glucose concentrations were recorded within 1 hour after admission. This study found that the blood glucose concentration was significantly associated with *severity* of head trauma in dogs and cats and was significantly higher in dogs and cats with head trauma than in the control animals. However, blood glucose concentration was not associated with *outcome*, which is divergent from human studies. This study may differ from human medicine in that overall cognitive function varies between veterinary and human patients (ie, our patients don't read!). These studies reiterate the importance that iatrogenic hyperglycemia should be *avoided* in patients with head trauma or cerebral ischemia (ie, seizuring dog, brain tumor patient) and that severe hyperglycemia in head trauma should potentially be treated with regular insulin therapy if warranted. When in doubt, it is best to withhold steroid therapy in head trauma patients to prevent hyperglycemia and other detrimental effects. Rather, osmotic agents such as mannitol have been found to be more beneficial to help decrease intracranial pressure.

Therapeutics to consider in head trauma patients *instead* of steroids include:

- Aggressive fluid resuscitation to help normalize or maintain blood pressure and maximize perfusion
- Oxygen therapy
- 15-30° head elevation
- Minimal jugular restraint or pressure
- Tight glycemic control

If IV fluid resuscitation alone does not help dilute and lower the glucose in hyperglycemic patients with head trauma, low dose 0.2 U/kg of regular insulin should be given IM every 2 to 4 hours for the first few hours to help lower blood glucose. This should be monitored frequently to ensure that the patient's blood sugar improves or that the patient does not become hypoglycemic, which would make neurologic monitoring even more difficult to evaluate.

Clinical Application

- Consider using mannitol at 0.5–2 g/kg IV over 20 to 30 minutes as needed for head trauma rather than steroids. This is particularly important if the patient develops "Cushings" reflex (ie, bradycardia with

concurrent hypertension), which is suggestive of severe cerebral edema and imminent herniation.
- Don't use steroids with head trauma until we have further evidence. Rather, use supportive care to increase perfusion to brain tissue (ie, IV fluids, oxygen) while decreasing intracranial pressure (ie, mannitol, head elevation)

NEW ANTI-INFLAMMATORY VERSUS IMMUNOSUPPRESSIVE DOSES OF STEROIDS

Traditionally, "shock doses" of steroids have been listed in emergency books at 4 to 6 mg/kg. Criticalists have moved away from giving steroids with trauma, due to potentially deleterious effects listed above. More recently, we have moved to different *doses* of dexamethasone sodium phosphate (DexSP). Anti-inflammatory doses of DexSP are generally considered 0.1 mg/kg, while immunosuppressive doses are as little as 0.25 mg/kg IV every 12 hours. For that reason, the 4 to 6 mg/kg dose in shock is no longer indicated. Remember that DexSP is approximately 8 to 15 times stronger than prednisone, so it is unlikely you need 40 mg/kg of prednisone with trauma!

Clinical Application

- Consider using low-dose DexSP for immunosuppression at the dose 0.25 mg/kg IV every 12 hours.
- Avoid the "shock doses" of steroids – if you are giving more than a few cc's, it's too much!
- While this newer dose of DexSP dose is lower, concurrent use of NSAIDS should still be avoided to minimize gastrointestinal effects.

DEXTROSE IN IV FLUIDS IS ALWAYS WARRANTED IN HOSPITALIZED ANIMALS TO HELP MAINTAIN NUTRITION

Dextrose supplementation in IV fluids is always warranted in ***hypoglycemic*** patients. However, in patients who are ***euglycemic***, the use of dextrose supplementation is not warranted, even for nutritional support. Why is extra dextrose bad? Recently, studies have shown that the effects of hyperglycemia are deleterious – in other words, increased insulin resistance may have secondary immunosuppressive effects. In addition, critically ill patients may already be hyperglycemic due to circulating excessive stress hormones such as glucocorticoids, catecholamines, and cytokines. Tighter glycemic control may help prevent cellular hypoxia by reducing endothelial damage and preventing cytopathic hypoxia. Human medicine (Van Den Berghe et al, NEJM 2001;345:1359-1367) recently found that intensive insulin therapy should be implemented in critically ill surgical ICU patients to prevent or treat hyperglycemia in *non*-diabetic patients, as *tight glycemic control* improved survival significantly. When intensive CRI regular insulin was used to maintain blood glucose between 80 and110 mg/dL, intensive insulin therapy reduced mortality during intensive care from 8.0% with conventional treatment to 4.6% ($P<0.04$). This was most significant in patients who stayed in ICU for > 5 days, and greatly reduced mortality from multiple-organ failure (MOF) with a proven septic focus. Overall, intensive insulin therapy "reduced overall in-hospital mortality by 34%, bloodstream infections by 46%, acute renal failure requiring dialysis or hemofiltration by 41%, the median number of red-cell transfusions by 50%... and patients receiving intensive therapy were less likely to require prolonged mechanical ventilation and intensive care."

How can we clinically apply this to veterinary medicine? The following steps should be considered when evaluating a critically ill hyperglycemic patient. First, diabetes mellitus (DM) must be ruled out. The diagnosis of DM should be supported based on the following: a urinalysis with evidence of glucosuria, clinical signs of pu/pd and weight loss, and persistent hyperglycemia and glucosuria on recheck. Second, considerations for hyperglycemia (non-diabetic in origin, such as stress hyperglycemia or severe hypoperfusion/hypovolemia) must be ruled out and treated appropriately. Like humans, dogs do not usually develop a stress hyperglycemia like cats. Rarely, dogs may develop the "stress of death" (SOD) hyperglycemia from *severe* shock and hypovolemia; if this is noted in dogs (ie, glucose > 160 mg/dL), patients should be thoroughly evaluated and volume resuscitated appropriately (once cardiogenic shock has been ruled out). Knowing that dogs only show a SOD hyperglycemia when they are potentially peri-arrest, it is imperative to consider aggressive resuscitation, if indicated. This SOD hyperglycemia should be treated with medical management first; if the hyperglycemia does not improve after several hours, the use of tight glycemic control with regular insulin therapy may be warranted. Finally, once treatment modalities have been initiated (such as IV fluid resuscitation, oxygen therapy, etc.), the use of regular insulin therapy can be considered with persistent hyperglycemia. It is important to reiterate that the theory of *tight glycemic control* may be more applicable in *dogs* pending more veterinary clinical research, as cats traditionally have a more profound stress hyperglycemia.

Finally, dextrose supplementation for nutritional support is not warranted, as it is not highly effective. If 5% dextrose is supplemented in 1 liter of fluids, it only provides 170 kcals/liter. For example, a typical 5 kg cat on IV fluids at 20 mL/hour will only receive 480 mL of fluids over the course of 24 hours, which amounts to only 80 kcal of nutritional supplementation within a 24-hour period. This cat's average nutritional requirement is approximately 220 kcals/day, and dextrose supplementation alone would fall significantly short of this. Increasing the fluid rate would potentially fluid overload the cat in an attempt to provide nutritional support (requiring 3 times maintenance!). Nor does this mean to add more dextrose into 1 liter of fluids, as this would significantly change the osmolality of the crystalloid and potentially become too hypertonic to deliver through a short-term peripheral catheter. We know that dextrose supplementation in IV fluids does not supplement enough RER, and we know that hyperglycemia in human medicine is associated with a higher mortality. Therefore, we should avoid over-supplementing dextrose to our patients who are able to maintain their own blood glucose.

Clinical Application

- In documented *hypoglycemia*, use IV boluses of dextrose (ie, 0.5 to 1.5 mL/kg of 50% dextrose, diluted 1:3 with saline) followed by a CRI of dextrose therapy until the animal is *euglycemic*.
- In patients that are already euglycemic, do not use routine dextrose supplementation to provide RER.
- Avoid supplementation > 5% dextrose through a peripheral catheter due to hyperosmolality, which would result in irritation to the vessel.
- In non-diabetic canine patients who are hyperglycemic (potentially from catecholamine release, stress, etc.), monitor the blood glucose. If it is persistently high (> 160 mg/dL), consider low dose regular insulin (IM) once the patient has been volume resuscitated or treated appropriately.

SEPTIC, SHOCKY CATS LOOK JUST LIKE SEPTIC, SHOCKY DOGS

Cats will be cats, and of course, have to do things differently! Cats have a unique physiologic response to shock, and it is often very different from their canine companion. The classic hyperdynamic shock state is rarely seen in cats (ie, brick, red, injected mm, tachycardia, bounding, pulses, etc.). Brady et al evaluated cats confirmed to have severe sepsis (based on necropsy findings) and evaluated pertinent history, physical examination findings, and results of hematologic and biochemical testing (n= 29 cats). Clinically, these septic cats were diagnosed with the following diseases: pyothorax, septic peritonitis, bacteremia secondary to gastrointestinal tract disease, pneumonia, endocarditis, pyelonephritis, osteomyelitis, pyometra, and bite wounds. In this study, clinical signs of severe sepsis in cats included physical examination findings such as lethargy, pale mucous membranes, poor pulse quality, tachypnea, hypo- or hyperthermia, signs of diffuse pain on abdominal palpation, bradycardia, and icterus. In addition, clinicopathologic abnormalities found in severe sepsis in cats included: anemia, thrombocytopenia, band neutrophilia, hypoalbuminemia, low serum alkaline phosphatase activity, and hyperbilirubinemia. This study showed how severe sepsis in cats is clinically different from canine patients with sepsis. Cats were characterized by lethargy, pale mucous membranes, signs of diffuse abdominal pain, tachypnea, bradycardia, weak pulses, anemia, hypoalbuminemia, hypothermia, and icterus. In other words, *septic cats are cold, flat, and bradycardiac*! The cause for the bradycardia is unknown, but factors such as parasympathetic stimulation, cytokine-induced myocardial depression (from myocardial depressant factor), and resistance to catecholamines (especially when hypothermic) are all proposed. Nevertheless, a sick, bradycardiac cat should make you *more* worried than a tachycardiac cat!

Clinical Application

- Bradycardiac cats should worry you more than tachycardiac cats!
- Search for causes of sepsis in bradycardiac, lethargic, pale cold cats.
- Consider doing tests such as CBC/CHEM/full body radiographs/UA/urine culture, routine abdominocentesis (or abdominal ultrasound) in this cat population to rapidly identify a cause for sepsis.
- Remember that cats show sepsis very differently from dogs.

VPCS SHOULD ALWAYS BE TREATED WITH LIDOCAINE OR PROCAINAMIDE

As with all drugs and pharmokinetics, there are pros and cons of using certain drugs. Anti-arrhythmic drug therapy is certainly beneficial in certain circumstances, as they may decrease the heart rate allowing for more time for ventricular filling (ie, beta blockers), and have mild anti-inflammatory properties (ie, lidocaine). However, with these same drugs come detrimental effects such as negative ionotropic effects, decrease myocardial function, increased requirement for defibrillation, and increased myocardial oxygen demand. Anti-arrhythmics can also be arrhythmiogenic in origin. In general, anti-arrhythmic therapy is warranted when patients have evidence of the following signs of poor perfusion: cold peripheral limbs, poor CRT, a prolonged CRT > 2.5 seconds, or tachycardiac > 170 (dogs) or >240 (cats). Similarly, if the ECG shows changes of malignancy such as "R on T" phenomenon, one should promptly consider anti-arrhythmics due to the increased risk of ventricular fibrillation. Finally, if the heart rate (HR) is > 170 to 180, one must investigate causes for tachycardia. The following step-wise problem tree should be considered with tachycardia:

- Immediately check a blood pressure (BP).
- If the BP is low (MAP < 60), consider a bolus of crystalloids (ie, LRS, Norm-R, saline) at 20 mL/kg IV over 15 to 20 minutes to see if this improves both the HR and the BP.
    - If it does improve, this tachycardia was likely due to hypovolemia.
    - A secondary bolus of crystalloid (or even a 5 mL/kg bolus of Hetastarch) can also be considered if mild to moderate improvement is shown, but the HR is still not within the normal range.
- If HR is > 170 to 180 (canine) and the BP is normal to slightly hypertensive, rule out pain.
- Consider analgesics
    - Hydromorphone at 0.1 mg/kg IV once, repeating every 4 to 6 hours as needed.
- If neither a fluid bolus or pain medication improve the HR, rule out the following causes for tachycardia and arrhythmias:
    - Electrolyte abnormalities
        - Blood gas
        - Treatment: potassium or magnesium supplementation, as indicated

- Hypoxia
  - Arterial blood gas or
  - Pulse oximeter
  - Treatment:
    - Oxygen supplementation
    - Treatment of underlying parenchymal lung disease
    - Reversal of sedation if hypoventilating (high PCO_2)
- Acidosis
  - Venous or arterial blood gas
  - Treatment: increase perfusion with IV fluids, if indicated
- Anemia
  - Packed cell volume
  - Treatment: IV fluid therapy (ie, crystalloids, colloids, blood products)

If, despite all these pro-active measures, the patient is still demonstrating tachycardia and arrhythmias, and if perfusion is compromised or the arrhythmia looks malignant on ECG, consider anti-arrhythmics:

- Lidocaine (1–4 mg/kg, IV, slow, followed by a CRI 25–50 µg/kg/min) should be promptly initiated (if ventricular in origin). Lidocaine is unlikely to have a beneficial effect in supraventricular arrhythmias, and its use should be reserved for arrhythmias ventricular in origin.
- Procainamide: if lidocaine appears to be ineffective (6–8 mg/kg IV slow over 5 minutes, followed by a CRI 25–40 µg/kg/min)

Clinical Application

- Evaluate patients for perfusion. If signs of poor perfusion are evident, these patients should be clinically treated for their poor perfusion, and treated with anti-arrhythmics if indicated.
- If patients show signs of good perfusion (ie, pink mm, strong synchronous pulses, CRT < 2 seconds, no pulse deficits), anti-arrhythmic therapy is not warranted.
- Treat the patient, not the arrhythmia or ECG!

ANALGESICS SHOULD BE WITHHELD IN CRITICALLY ILL PATIENTS BECAUSE IT CAUSES RESPIRATORY DEPRESSION

In the emergency room and ICU, we see patients who may have undergone thoracic trauma from bite wounds, contusions, pneumothorax, diaphragmatic hernias, rib fractures, etc. Other patients may have underlying pneumonia, congestive heart failure, or lung disease, or may be hypoventilating from pain or anesthesia. Often times, these patients have concurrent fractures which may be painful, and analgesia therapy should *not* be withheld in these patients. Many veterinarians are hesitant to use opioids in these critically ill patients due to the fear of hypoventilation or respiratory arrest. While it is imperative that these patients be monitored carefully, one should not hesitate to provide analgesia to these patients. Patients should be adequately volume resuscitated (once cardiogenic shock has been ruled out) first to maintain normal perfusion, treated with oxygen therapy if hypoxic, and then administrated analgesics once the patient has been assessed for neurologic function (with trauma cases).

A study by Berg and Orton evaluated arterial blood gases in patients underlying intercostal thoracotomy; these patients were treated with morphine and oxymorphone, and while hypoventilation was documented based on rising pCO_2, this was not clinically significant. Based on the paucity of literature showing respiratory depression from opioids, analgesic therapy should not be withheld from patients with lung disease. When in doubt, it is best to slowly titrated drugs to effect.

Clinical Application

- Patients should be treated aggressively to maintain oxygenation and perfusion with oxygen supplementation and carefully titrated pain control.
- Consider the following opioids and doses:
  - Hydromorphone: 0.1 mg/kg IV q 6 hours
  - Morphine: 0.5 mg/kg IM or SC q 3 to 4 hours
  - Fentanyl: 1–5 µg/kg/hour, followed by CRI
  - Torbugesic: 0.1–0.2 mg/kg IV q 1 or 0.2 hours to 0.4 mg/kg SC or IM every 1 to 2 hours
- Continue to carefully monitor tachypneic or dyspneic patients with pulse oximetry, respiratory rate and effort monitoring, arterial blood gas analysis, etc.
- When concerned about analgesic therapy in critically ill patients, consider *reversible* drugs in the event of an emergency. Reverse with: Naloxone 11–22 µg/kg IV or IM as needed (0.5–1 mL per dog!)
- Consider lidocaine patches over rib fractures, sternotomy sites, or flail chest sites. These can be safely used in both dogs and cats concurrently with opioids or NSAID therapy.

IV FLUIDS: DOES IT MATTER WHAT BAG I GRAB?

Recently, there has been discussion about what the safest IV fluid bag to grab is. Does it matter if you stock LRS vs. 0.9% saline vs. Norm-R vs. Plasmalyte on your shelves? In the event of an emergency, does it really matter? Recently, the misconception that LRS is always the safest choice for fluid therapy has been debated. When it comes down to it, most crystalloids are safe in replacing what you need with either dehydration or shock: free water and salt. Most of these balanced replacement or maintenance crystalloids provide a sodium level similar to the body, and for that reason, it is generally safe to go with the decision to pick an IV fluid choice closest to your patient's sodium.

LRS, a crystalloid replacement fluid, has a pH of 6.5, a Na^+ of 130 mEq/L, 4 mEq/L of K^+, and a Cl^- of 109 mEq/L. In addition, it has minimal Ca^{++} at 3 mEq/L. It also provides 28 mEq/L of lactate which is metabolized by the liver into bicarbonate to act as a safe buffer. It is important, however, to note that not all lactates are created equal! Lactate is available in two mirror images:

L-lactate ("L" for "living", as this is the enatiomer or version that our cells produce and utilize) and D-lactate ("D" for dead, the bad lactate). Both forms of lactate are present (50/50 mix) in LRS. It is been reported that the D-lactate can potentially promote inflammation by activating neutrophils and increasing the stickiness of endothelial cells. Lo and behold, saline, Hetastarch, and Dextran 40 can also increase neutrophil activation to a greater degree than LRS. While "pure" L-lactated Ringer's (with no bad D-isomer) is available from Baxter, remember that with day to day use, LRS is usually a safe fluid of choice. Not only is it balanced, but it provides small amounts of calcium and potassium. In clinical cases of hypocalcemia or hypokalemia however, additional supplementation is usually necessary. Secondly, LRS is considered an alkalinizing fluid due to the bicarbonate precursor lactate, and this is beneficial in patients who may have an underlying metabolic acidosis (i.e., from renal failure, ethylene glycol toxicity, lactic acidosis, or diabetic ketoacidotic state). The three main contraindications for using LRS are: liver failure, lymphosarcoma (LSA), and blood transfusions. Since lactate is metabolized by the liver to bicarbonate, metabolism may be compromised in patients with cirrhosis, icterus, portosystemic shunts, or underlying affected liver metabolism. Therefore, LRS should not be used in any patients with underlying liver disease. Secondly, patients with lymphosarcoma have been noted to be hyperlactatemic and have a decreased ability to metabolize lactate compared to normal dogs. This may be due to an increased preference for tumor cells to utilize glucose for energy via anaerobic metabolism, which results in the production of lactate. Lastly, patients requiring blood transfusions should not have the transfusion administered with LRS, as the small amount of calcium in LRS may bind with the citrate, resulting in micro- or macro- agglutination by activation of the clotting cascade.

Clinical Application

- When in doubt, any balanced replacement or maintenance crystalloid (ie, LRS, 0.9% NaCl, Norm-R, or Plasmalyte-148) is effective for volume replacement.
- In cases of liver failure, blood transfusion, or lymphosarcoma, LRS is contraindicated.
- If a blood transfusion is to be given, it should only be given with 0.9% NaCl.
- Chose a fluid choice with a sodium closest to your patient's sodium.

CONCLUSIONS

With the implementation of both clinical research and scientific research, improvement in treatment modalities have improved the overall quality of care and outcome in critically ill veterinary patients. Advances should be frequently updated in order to avoid perpetuating outdated modalities. Veterinarians can easily improve outcome with updated techniques which require simple diagnostics such as glucometers, opioid pain control, physical examination monitoring, and supportive care.

References are available from the author upon request.

CURRENT CONCEPTS IN CPR

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Cardiopulmonary resuscitation (CPR), or the more comprehensive term *cardiopulmonary cerebral resuscitation* (CPCR), is still one of the most important interventions performed in human or veterinary medicine. This is especially true in veterinary medicine when dealing with emergency and critical critically ill patients. Although not performed frequently, it must be utilized in the appropriate situation and using the most effective techniques in order to maximize the possibility of success. Currently estimates of successful CPR in veterinary patients are reported to be less than 10% but this may vary from institution to institution. This figure compares favorably with survival rates reported for out of hospital cardiopulmonary arrest in human patients but is lower than reported survival rates for in-hospital arrests.

ADVANCE DIRECTIVES

Advance directives are a formal component of human medicine and have gained more importance in veterinary medicine. In generic terms, advance directives refer to information provided to a physician by a patient detailing what care should be provided if the patient is unable to make decisions. In veterinary patients, this equates to the primary care clinician having a detailed discussion with the pet owner concerning medical management of a pet who has had a life-threatening medical event. In more general terms and for the purpose of this discussion, this addresses whether the patient should be resuscitated if cardiopulmonary arrest occurs. This discussion should be documented in the medical record. There should be a way of identifying which patients have "do not attempt resuscitation" (DNAR) orders and the nursing staff and all clinicians should be made aware of these orders.

COMPARATIVE CPR

The American Heart Association published new guidelines in 2000 for cardiopulmonary resuscitation and emergency cardiovascular care. These guidelines represented significant changes in protocols that should not be immediately extrapolated to veterinary patients. The most significant changes included the incorporation of immediate electrical defibrillation into Basic Life Support (BLS). Previous to this recommendation, BLS included **A**, **B**, **C**, **A**irway, **B**reathing and **C**irculation. **D**efibrillation was included in Advanced Life Support (ALS). The successful impact of rapid electrical defibrillation on survival in patients with cardiopulmonary arrest led to this change in recommendations. The overall impact of this recommendation has been the increased availability and access to automated external defibrillators (AED). This technology allows minimally trained lay rescuers as well as trained rescuers the ability to defibrillate patients with ventricular fibrillation. The emphasis on early defibrillation is based on reports that as many as 70% of people in the United States who experience out of hospital cardiopulmonary arrest are initially in ventricular fibrillation.

Although ventricular fibrillation does occur in dogs and rarely in cats, it is not necessarily the most common rhythm disturbance recognized and is not recognized in the majority of veterinary patients who experience cardiopulmonary arrest.

It has also been found that what would be considered standard drug therapy in veterinary patients, utilizing epinephrine and atropine, has not significantly improved survival in people and therefore these drugs are considered marginal. These drugs would still be considered the cornerstone of therapy for veterinary CPR.

TECHNIQUES

Basic Life Support

In veterinary medicine basic life support (BLS) or basic CPR is still considered the **A**, **B**, **C**'s (**A**irway, **B**reathing, and **C**irculation). Due to the limited access to defibrillators in veterinary practice and the nature of the underlying diseases contributing to cardiopulmonary arrest in veterinary patients, it is unlikely that this will change. It is also important for the veterinary clinician to recognize that many dysrhythmias occur in the critically ill dog and cat. We cannot extrapolate the information that approximately 70% of people who experience cardiopulmonary arrest out of hospital have ventricular fibrillation as their initial rhythm. The common dysrhythmias associated with cardiopulmonary arrest in dogs and cats include, ventricular asystole, pulseless electrical activity (PEA) (formerly known as electrical mechanical dissociation (EMD) and ventricular fibrillation. Therefore the utility of early defibrillation in veterinary patients is unknown unless the patient has documented ventricular fibrillation.

Current recommendations for veterinary BLS include assessing and providing an airway if required, assessing and providing breathing if required and assessing and providing circulation if required.

Airway: Although there are no real changes in the recommendations for this procedure, the priority is to establish an airway. In most cases this is accomplished by per oral endotracheal intubation. Confirmation of correct tube placement is recommended by visual assessment, digital palpation and/or by $ETCO_2$ monitoring. It has been suggested that airway be prioritized below circulation and breathing. In this scenario rather than A, B, C, the priority would be C, A, B. If following this protocol, external thoracic compressions should be started immediately and prior to providing an airway. This recommendation is based on research performed to evaluate bystander (out of hospital) CPR. In some experimental animal models, most notably pigs, it has been shown that animals can be resuscitated from ventricular fibrillation by only performing chest compressions. It has been hypothesized that when performing external chest compressions, enough passive ventilation occurs for the patient to survive. Another important factor is that during ventricular fibrillation, oxygen delivery is dependent on blood flow, not ventilation.

Breathing: The only innovations with breathing have been the use of simultaneous compression ventilation protocols by some clinicians. When utilizing the thoracic pump theory, it has been demonstrated in animal models that cardiac output can be improved by increasing intrathoracic pressure. Conventional external thoracic compressions utilize the cardiac pump theory in combination with interposed respirations. The cardiac pump involves direct compression of the myocardium to promote cardiac output. The thoracic pump utilizes compression of the thoracic cavity to indirectly improve cardiac output by effecting blood flow through the giant vessels. The incorporation of simultaneous ventilations dramatically increases intrathoracic pressure. There are however, potential complications associated with this technique, which include barotrauma and pulmonary contusions. The target for breathing rate should be 15-20 breaths per minute.

Circulation: The circulation component of BLS has not changed significantly and has been discussed in part under the breathing section with reference to simultaneous compression and ventilation protocols. There are currently two theories explaining the mechanisms of cardiac out during external thoracic compressions. The cardiac pump theory suggests that direct compression of the myocardium accounts for the majority of cardiac output. In veterinary patients this would apply in patients with body weights of < 7 kg. In patients with body weights of > 7 kg, the thoracic pump would better explain cardiac output. The latter suggests that compressions of the widest portion of the thorax increase intrathoracic pressures, which indirectly leads to increased cardiac output. This may be combined with simultaneous ventilation, which should further increase intrathoracic pressures. The target for chest compressions should be 100 beats per minute. The use of interposed abdominal compressions during CPR has become more common and has been shown to increase venous return by up to 25%.

Advanced Cardiac Life Support

In veterinary medicine, advanced life support (ALS) has included all procedures outside of BLS. So the pneumonic of **D**, **E**, **F** still applies.

Drugs: Although there are no longer strong recommendations for epinephrine and atropine for therapy of cardiopulmonary arrest in people, these drugs still play a valuable role in veterinary CPR. The most commonly reported dysrhythmias identified during cardiopulmonary arrest in the dogs and cats are bradyarrhythmias, asystole and pulseless electrical activity (PEA) formerly known as electrical mechanical dissociation. Atropine and epinephrine may be useful for management of these dysrhythmias. The current recommendation for the use of epinephrine is using the low dose protocol (0.01–0.02 mg/kg). This protocol calls for the use of the standard concentration of epinephrine (1:1000) diluted 10-fold and administered at a volume of 1 mL/10 kg of body weight. This is compared with the high dose epinephrine protocol which utilizes the same volume administered (1 mL/10 kg) but using the 1:1000 dilution epinephrine straight from the bottle. There is some renewed interest in the use of vasopressin and recent publications have shown some increase in survival in people who have failed conventional medical therapy. Vasopressin can be administered at a dosage of 0.8 U/kg. This equates to approximately 0.5 mL/10 kg of body weight. The advantage of vasopressin may be its performance in the face of hypoxia and acidemia. In addition its mechanism of action is via direct stimulation of receptors in vascular smooth muscle and it does not appear to increase myocardial oxygen consumption. Atropine is still administered at 0.04 mg/kg or approximately 1 mL/10 kg body weight.

Routes of administration that are recommended include intravenous through a central line, intravenous via a peripheral line with bolus to follow, intraosseous administration and intratracheal administration. The drugs that can be safely administered via the intratracheal route can be remembered by the pneumonic **NAVLE** and include **N**aloxone, **A**tropine, **V**asopressin, **L**idocaine, and **E**pinephrine. The doses should be twice the intravenous dose and should be diluted in sterile water.

ECG: In veterinary CPR it is still imperative to know what dysrhythmia is present. Because it is difficult to predict which rhythm is present, intervention and outcome will be dependent on this diagnosis. The most common reported dysthymias include ventricular asystole, PEA and ventricular fibrillation.

Fibrillation control: Defibrillation is prioritized lower and still included in ALS for veterinary patients for two reasons. First and foremost, patients must be in ventricular fibrillation for this intervention to be utilized. Second, it still appears that many veterinary hospitals do not have access to this equipment. The advances in the area of defibrillation are the use of biphasic defibrillators, which may be more effective than the monophasic defibrillators.

Fluid resuscitation: Fluid resuscitation should be a component of CPR. However, aggressive volume expansion should only be utilized if it is suspected that volume depletion has contributed to the cardiopulmonary arrest. Volume overload can have detrimental effects on these patients. An increase in central venous pressure and right sided pressures may lead to reduced coronary perfusion pressures.

MONITORING

Monitoring of patients during CPR is imperative but difficult. Physical examination along with palpation of peripheral pulses, venous blood gas analysis and end tidal capnography are the most reliable tools. Other suggested techniques include the use of a Doppler blood pressure probe on the cornea to evaluate cerebral artery perfusion but this is unreliable in the author's experience. Return of spontaneous ventilation is often a limiting step, as it appears that return to spontaneous circulation occurs more commonly. The frequent cessation of external thoracic compressions in order to examine the ECG or auscultate the thorax may lead to decreased success.

POST-RESUSCITATIVE CARE

Due to poor survival rates, it is often unexpected that post-resuscitative care is required. It is however imperative that the clinician anticipate survival so this care can be provided immediately. If post-resuscitative care cannot be provided then the CPR was wasted. Post-resuscitative care is primarily symptomatic and is dependent on close monitoring and excellent nursing care. Oxygen supplementation should be considered in all of these patients and ventilatory support may also be required. Fluid therapy should be continued as required and inotropic and pressor therapy may be indicated to maintain mean arterial pressures. Neurologic dysfunction may be common following resuscitation and infusion of mannitol at 0.5 to 1 g/kg over 30 minutes may help treat cerebral edema and has free radical scavenging properties. It has also been demonstrated that hyperglycemia may have a negative impact on outcome and therefore should be monitored. Due to the lack of evidence for their use, corticosteroids should be avoided. If possible prognosis should not be based on neurologic signs within the first 24 to 48 hours due to the possibility of significant change. Nutritional support via feeding tubes or total parenteral nutrition should be provided if patients have not returned to reasonable function within 48 to 72 hours.

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EMERGENCY MANAGEMENT OF THE PATIENT WITH HEATSTROKE

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Heatstroke occurs when the elevation of the body's temperature, due to environmental heat stress, exceeds the cooling capacity of compensatory mechanisms. With heatstroke the cells literally cook. This causes thermal damage to the hypothalamic thermoregulatory centers that will further elevate the body temperature. This can be complicated by disseminated intravascular coagulation initiated by disrupted vascular endothelium, which compounds the global pathology. Classically, central nervous system dysfunction is always evident while markedly elevated liver enzyme levels are typical clinicopathologic abnormalities.

There are two main types of heatstroke: classic and exertional. Classic heatstroke is associated with impaired compensatory mechanisms. It usually affects elderly or disabled humans who experience prolonged exposure to hot and humid conditions. It is of gradual onset over a period of hours to days.

Exertional heatstroke occurs in individuals with normal compensatory mechanisms who are exposed to overwhelming heat stress. Its clinical features include: 1) rapid onset CNS dysfunction associated with stupor, delirium, focal deficits, and seizures, 2) history of exposure, 3) warm skin, 4) tachypnea, often from edema or hemorrhage, and 5) vomiting and diarrhea. Gastrointestinal hemorrhage can result from disseminated intravascular coagulation (DIC).

PATHOPHYSIOLOGY

Acute Phase Response

The body has a protective acute phase response to heat stress that is a coordinated reaction that involves endothelial cells, leukocytes, and epithelial cells that protect against tissue injury and promote repair. The interleukin-6 produced during heat stress modulates local and systemic acute inflammation responses by controlling the levels of inflammatory cytokines. Interleukin-6 also stimulates hepatic production of anti-inflammatory acute-phase proteins, which inhibit the production of reactive oxygen species and the release of proteolytic enzymes from activated leukocytes. Other acute-phase proteins stimulate endothelial-cell adhesion, proliferation, and angiogenesis, thus contributing to repair and healing.

Experimental heatstroke models show local and system insults associated with heat stress, such as splanchnic hypoperfusion and altered immunologic and barrier functions of the intestines. This allows for leakage of endotoxins, increased production of inflammatory cytokines, and the release of endothelial vasoactive factors such as nitric oxide and endothelins.

Heatstroke and its progression to multiple organ dysfunction syndrome (MODS) are due to a complex interaction between hypocirculatory function, the direct cytotoxicity of heat, and the inflammatory and coagulation responses of the host. These even lead to altered blood flow in the microcirculation which results in injury to the vascular endothelium and tissues.

Cytokines

The inflammatory cytokines that are elevated include tumor necrosis factor-α (TNFα), interleukin IP, and interferon-gamma. The anti-inflammatory cytokines that are elevated include interleukin-6, soluble TNF receptors p55 and p75, and interleukin-10. An imbalance between the two types of cytokines may result in either inflammation-associated injury or refractory immunosuppression.

Coagulation-Cell Injury and Endothelial-Cell Injury

Endothelial cell injury and diffuse microvascular thrombosis are prominent features of heatstroke. Therefore, DIC and alterations in the vascular endothelium may be important pathologic mechanisms in heatstroke. Normalization of the core temperature inhibits fibrinolysis but not the coagulation aspects of DIC.

The hemodynamic changes are characterized as a high output vasodilated state. The patient might not be significantly volume depleted, but instead have a near-normal volume that is physiologically shunted to the periphery. The central venous pressure and left ventricular filling pressure are usually midrange to low and rise upon cooling. Hypotension is common and is usually not a consequence to fluid depletion but rather to high output heart failure.

In humans, certain cardiopulmonary changes occur in heatstroke. Electrocardiographic abnormalities include ST depression, T inversion, QT prolongation, and intraventricular conduction delays. These changes are attributed to myocardial hemorrhage which can resolve and allow the EKG to return to normal. Pulmonary edema is an occasional complication caused by thermal injury to vascular endothelium, myocardial dysfunction, return of large volumes of plasma to the central circulation after cooling, cutaneous vasoconstriction, and the adult respiratory distress syndrome.

Thermal toxicity can involve the brain to cause brain cell death, cerebral edema, and local hemorrhage to lead to stupor and coma. Early changes can be reversed with prompt treatment.

Acute renal failure affects 35% of human cases. Contributing factors include thermal injury, hypotension, and shock from cardiovascular collapse and rhabdomyolysis. It is therapeutically important to promote continuous urine flow with intravenous fluids, mannitol, and furosemide, if necessary.

The clinical pathology changes can be extensive and include marked elevations in the liver enzymes (alanine aminotransferase [ALT], aspartate aminotransferase [AST], lactate dehydrogenase [LDH]) and creatine kinase, and decreased PaO_2 with a mixed metabolic acidosis/respiratory alkalosis. The urinalysis changes often include myoglobinuria, pigment casts from rhabdomyolysis, RBCs, and protein. The serum calcium level is usually normal. It might decrease initially due to calcium deposition in injured muscle and then rebound 2 to 3 days later to hypercalcemia after the calcium deposits dissolve.

The hemogram changes can include leukocytosis, hemoconcentration, and anemia if a hemorrhagic diathesis occurs. Disseminated intravascular coagulation occurs commonly with severe heatstroke and is associated with prolonged prothrombin time (PT)/partial thromboplastin time (PTT), hypofibrinogenemia, thrombocytopenia, and positive fibrin split products. It is caused by thermal activation of platelets and clotting factors, heat-induced liver failure and impaired coagulation factor synthesis, and activation of the clotting cascade by vascular endothelial damage and generalized cell necrosis. DIC will increase mortality associated with heatstroke. Heparin therapy is controversial, but has been associated with recovery.

The most serious complication of heatstroke involves MODS. These include encephalopathy, rhabdomyolysis, acute renal failure, hepatocellular injury, intestinal ischemia or infarction, pancreatic injury, and hemorrhagic complications, especially DIC.

TREATMENT

The therapeutic outcome with heatstroke patients is directly related to the duration of exposure of tissues to high temperatures. Immediate cooling is paramount and should begin at the same time as general stabilization measures are undertaken. Field cooling may be accomplished by splashing or spraying water over the patient, while using any means of obtaining airflow. Once the patient has arrived at the hospital, other cooling measures can commence. Ice bath immersion has recently been viewed with skepticism because conduction is a fairly inefficient mode of heat transfer compared with evaporation/convection. Furthermore, transfer of heat from the body core to the environment is dependent on the conductivity of the skin and subcutaneous tissues, which in turn depends on blood flow. Ice water immersion rapidly drops skin temperature, but the resulting vasoconstriction causes the skin and subcutaneous tissues to behave as an insulator, blocking heat transfer from the core. Lowered skin temperatures also result in shivering, which generates heat and further limits cooling. It is difficult to maintain monitoring devices on immersed patients.

The preferred cooling method involves the use of a lukewarm water spray along with fans. This method is not only practical, but it minimizes shivering, vasoconstriction, and discomfort. In dogs and cats, the cooling treatment process should be discontinued when the body temperature reaches 103°F in order to avoid iatrogenic hypothermia.

Other cooling methods include 1) cold IV lines and oxygen, which contribute little to heat transfer, and 2) high frequency jet ventilation, which increases evaporative heat loss from the respiratory tract by increased minute ventilation through the upper airway, and ice water gastric lavage. Ice water enemas are thought to be of little use and theoretically can cause water intoxication. ***Isopropyl alcohol soaks risk skin absorption and toxicity and are no longer considered in pediatric humans.*** The use of antipyretics (aspirin, acetaminophen) is irrational because these function through lowering of the hypothalamic thermoregulatory set point, which is inoperative in heatstroke.

Fluid therapy for the heatstroke patient should be adjusted to the patient's pathophysiologic status. If heat stroke occurred rapidly over a relatively short period of time just prior to its being presented for veterinary care, there will hardly be any significant dehydration. In such cases, the patient's blood pressure is the primary concern and crystalloid fluid therapy should be used according to its blood volume status. Hypotensive patients should receive a volume expanding dose of isotonic fluids such as lactated or acetated Ringer's. Although one whole blood volume of fluids (70–90 mL/kg for a dog and 35-40 mL/kg for a cat given over the first hour) is generally recommended for the treatment of a hypotensive crisis, close patient monitoring for intravascular fluid overload should be done every 15 minutes during that rapid phase of fluid administration. The heat stroke patient might be particularly predisposed to cardiopulmonary dysfunction thus making it prone to developing pulmonary edema from an excessive fluid delivery rate. Persistent hypotension after the administration of IV crystalloid will call for treatment with a colloid solution such as Hetastarch. Failure to hemodynamically stabilize the patient after this will call for vasopressor drug treatment using either dobutamine, dopamine or vasopressin.

Urine volume must be closely monitored because oliguric or polyuric acute renal failure can be a significant complicating factor. In the case of oliguria, attempts to improve urine output with the administration of furosemide (1–2 mg/kg IV) should be done because further fluid therapy will be more complicated if anuria occurs. In such cases, the dose of IV fluids will be measured against the measured urine output, insensible water losses (13–20 mL/kg/24 hours), and any other ongoing fluid losses as might occur with vomiting or diarrhea.

Patient monitoring for the most severe patient should be as physiologic as possible by using information that can be obtained with central venous pressure, arterial blood pressure, and urine output measurements. This will allow the clinician to alter the treatment according to the changing needs of the patient. A central intravenous line will facilitate the administration of medication as well as allow ready access for blood sample collections.

Broad-spectrum antibiotics are commonly provided to veterinary patients with heatstroke in order to cover for the transluminal migration of intestinal bacteria that can enter the systemic circulation subsequent to the breakdown of the bowel mucosal barrier. Broad-spectrum coverage is recommended because severe heat stroke and sepsis commonly coexist because of the above mechanism.

Alpha agonists should be avoided initially because they promote peripheral vasoconstriction that will prevent cooling. They can also cause further ischemia to already impaired organs such as the kidney or the liver. Dopamine and/or dobutamine, however, may be indicated for refractory hypotension.

Heparin is recommended for severe heatstroke. Plasma can also be given if abnormal bleeding is present. At first, an initial bolus dose of 75 to 100 units/kg can be administered intravenously. This is followed by subsequent doses of 75 to 100 units/kg every 8 hours delivered by slow intravenous infusion over each 8-hour period. If treatment is successful, the patient and its coagulation parameters should show improvement after 24 hours after which time the heparin dosage is tapered and discontinued over the subsequent 24-hour period.

PROGNOSIS

Morbidity and motility are directly related to the peak temperature and to the duration of time the elevated temperature persists. A delay in treatment for two hours or more may result in a 70% chance of death in humans. Prolonged coma of greater than four hours is also a poor prognostic factor.

GASPING CAT – APPROACH TO THE DYSPNEIC FELINE

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Thoracic disease in the cat can present as one of a multitude of disorders. Many of the problems are treatable pending a definitive diagnosis, while others are classified as non-treatable. It is important for the practitioner to accurately identify the exact disease process in order to implement what might end up to be life-saving treatment. On the other hand, the early recognition of a non-treatable disease in a dyspneic patient can avoid protracted suffering to the cat and excess expense to the client.

Dyspnea and tachypnea are the most characteristic signs of feline pulmonary and pleural diseases. Although coughing is a sign frequently associated with tracheal and bronchial disorders, the clinician should be aware that most feline pulmonary and pleural disorders are not associated with coughing. Because the dyspneic cat is often in critical status, the primary clinical objective is to expediently diagnose the cause and simultaneously provide supportive treatment.

The etiologies of respiratory embarrassment can involve lesions anywhere along the respiratory tract, pleural space, or heart. Therefore, it behooves the clinician to obtain a complete history and perform a detailed physical examination to accurately localize the primary lesion. Emergency situations might initially require an abbreviated history and physical followed by a more detailed study following the patient's stabilization.

The diagnosis of most thoracic diseases in the cat usually requires the use of diagnostic aids. Depending on the problem at hand, such tests might include: hemograms, serum biochemistry determinations, cytology and culture of respiratory secretions, serology, electrocardiography, tissue biopsy, and thoracic radiography. To avoid compounding the stress to the dyspneic cat, certain diagnostic procedures might have to await the clinical response to symptomatic emergency therapy in order to avoid iatrogenic complications. The criteria for classifying thoracic disease will vary among the internist, radiologist and pathologist.

Table 1. Characteristics of Some Disorders Causing Pulmonary Alveolar Infiltrates in the Cat

Disease	Predisposing or Direct Cause	Other Diagnostic Findings	Treatment Principles	Prognosis
Bacterial pneumonia	1. Viral respiratory infection 2. Aspiration 3. Primary/idiopathic	- Fever - Leukocytosis - Radiographic lobar involvement; ventral common - Tracheal wash cytology: WBCs, bacteria	1. Maintain hydration with parenteral fluids 2. Provide O_2 3. Antibiotics 4. Bronchodilating drugs	Fair to guarded
Chemical pneumonitis	1. Smoke inhalation 2, Aspiration of oral or gastric secretions	- History & physical findings obvious with smoke inhalation - Aspiration commonly occurs with altered consciousness or iatrogenic - Bacterial pneumonia commonly complicates	1. Assure patent upper airway 2. Broad spectrum antibiotics 3. Bronchodilating drugs	Fair to guarded
Cardiogenic pulmonary edema	1. Cardiomyopathy 2. Hyperthyroid-induced myocardial hypertrophy 3. Congenital 4. Acquired valvular disorders	- Characteristic auscultable findings: murmurs, gallop rhythm, arrhythmias - Radiographic cardiomegaly with pleural effusion or alveolar infiltrate - EKG & echocardiographic Changes	1. Provide O_2 2. Furosemide 3. Specific cardiac drugs depending on exact pathology	Guarded to grave
Noncardiogenic (neurogenic) pulmonary edema	1. Electrocution 2. Post seizure	- Electrocution: acute onset, oral burn, dorsocaudal radiographic pulmonary alveolar infiltrate - Post seizure	1. Furosemide 2. Provide O_2 cage 3. Avoid dehydration	Guarded to good

Table 2. Characteristics of Selected Feline Interstitial Lung Disease

Disease	Cause	Helpful Ancillary Clinical Findings	Treatment	Prognosis
Interstitial edema	1. Cardiomyopathy, & other causes of congestive heart failure 2. Noncardiogenic 1. Hypoalbuminemia 2. IV fluid overload 3. Electrocution 4. Viral infections 5. Toxic inhalants	Gallop rhythm, echo- & electrocardiographic abnormalities, cardiomegaly History of exposure to toxic inhalants, viral infections, iatrogenic fluid overload, electric cords	1. Diuretics, O_2, specific cardiac drugs such as digoxin or propranolol depending on type of cardiac pathology 2. Diuretics, O_2, removal of insulting agent, theophylline	(1) Guarded to grave (2) Good to poor depending on associated cause
Interstitial pneumonia	Viral respiratory disease	Fever, nasal discharge, sneezing, conjunctivitis, oral ulcerations, history of exposure to infected cats, viral isolation	Supportive: maintain hydration & nutrition, antibiotics for 2° bacterial complications	Good to fair
Granulomatous disease	Systemic mycoses, toxoplasmosis, irritating inhalants, immune-mediated disease	Knowledge of geographic origin where mycotic disease prevails; dietary & environmental history; presence of other coexisting organ abnormalities; serology; tissue biopsy	Toxoplasmosis:pyrimethamine & sulfadiazine; clindamycin Histoplasmosis & blastomycosis:- Itraconazole, amphotericin B Immune-mediated disease: immunosuppressants	Fair to grave
Pulmonary fibrosis	Healing phase of several disease processes; sometimes idiopathic; old age change	History of prior pulmonary inflammatory disease; normal hematologic & cytologic test results; sometimes history reveals chronic coughing; absence of other physical abnormalities	Bronchodilating drugs such as theophylline or aminophylline; occasional short-term use of gluco-corticoids. No reversal nor cure for pulmonary fibrosis.	Fair to poor
Metastatic lung neoplasia	Extrapulmonary source of malignant neoplasia, ie, mammary adenocarcinoma	Coughing is rare; location of primary source of neoplasia via physical exam, radiography, or surgery; tissue biopsy with histopathologic confirmation; needle aspiration cytology	Chemotherapy; surgical removal of primary tumor if indicated	Usually grave
Primary lung neoplasia	Example: bronchogenic carcinoma	Physical exam might reveal muffled chest sounds on involved side; radiography strongly suspicious; neoplastic cells on needle aspirate or surgical biopsy specimens; cough is rare unless there is bronchial impingement	Chemotherapy, surgical removal	Usually grave
Lung worms	Aleurostrongylosis	Mixed pattern on radiographs; findings of larval forms on fresh fecal smears & Behrman technique; coughing a common associated finding; eosinophilia on hemogram	(a) Levamizole - 20 to 30 mg/kg once every other day for five treatments (b) Fenbendazole 50 mg/kg/d x 3 d	Good
Lung fluke	*Paragonimus kellicotti*	Radiographs: solid or cavitated, circumscribed densities usually in caudal lobes; coughing common, fluke eggs on fecal, eosinophilia	(a) Albendazole- 50 mg/kg/d minimum of 14 days (b) Fenbendazole 50 mg/kg/d x 10 d (c) Praziquantel 25 mg/kg Q 8 h x 2 d	Good to fair
Heartworms	Dirofilaria immitis	Diffuse interstitial infiltrate; pulmonary artery enlargement; right heart enlargement; eosinophilia	Author does not recommend adulticide treatment; treat symptomatically with glucocorticoids & for heart failure (if present)	Guarded

Table 3. A Clinical Description of the Causes of Pleural Effusion in the Cat

Cause	Associated Physical Findings	Associated Clinical Findings	Fluid Type and Characteristics	Treatment	Prognosis
Congestive cardiomyopathy	- Dyspnea - Muffled chest sounds - Sometimes heart murmurs - Cardiac gallop rhythm - Rarely ascites - Occasionally aortic thrombo-embolism	(1) Characteristic electrocardiographic abnormalities (2) Oftentimes mild BUN elevations & moderate liver serum enzyme elevations (3) Radiographically generalized cardiomegaly with pulmonary interstitial or alveolar pattern along with pleural effusion	(1) Obstructive effusion (2) Serous, pseudochylous, or serosanguineous (3) Modified transudate (4) Cytology: initially mainly RBC's & lymphocytes with smaller numbers of neutrophils, macrophages, & mesothelial cells	(1) Removal of fluid by thoracentesis (2) O_2 (3) Diuretics (4) Digoxin (5) Taurine 500 mg bid	Guarded to grave
Lymphosarcoma	- Dyspnea - Muffled chest sounds (sometimes mainly anteriorly) - Noncompressible anterior thorax - Sometimes fever - Occasionally other organ involvement	(1) Sometimes anemia (2) Rarely lymphocytosis with anaplasia (3) (+) FeLV (4) Radiographically: anterior mediastinal mass causing tracheal elevation & posterior displacement of the heart (5) Ocular fundoscopic changes occasionally (6) Neoplastic lymphocytes on aspirate cytology of the mass (7) Rarely hypercalcemia	(1) Obstructive effusion (2) Serous or serosanguineous (3) Modified transudate or exudate (4) Cytology: anaplastic lymphocytes with mixture of RBC, mesothelial cells, macrophages & neutrophils	(1)Thoracocentesis (2) Chemotherapy	Guarded to grave
Pyothorax	- Dyspnea - Fever - Sometimes dehydration - Muffled chest sounds	(1) Leukocytosis with left shift (2) Radiographically: no cardiomegaly or thoracic masses; pleural thickening (3) Bacterial growth on culture (4) Possible restrictive lung disease	(1) Septic inflammatory (2) Purulent or sanguinopurulent (3) Pure exudate (4) Cytology: many neutrophils containing bacteria, free bacteria, toxic neutrophils, mononuclear cells	(1) Thoracocentesis (2) Thoracic lavage (3) Antibiotics	- Good to poor - Lung Abscess & chronic pleuritis are possible sequele
Infectious feline peritonitis – "wet-form"	- Dyspnea - Fever - Muffled chest sounds - Occasionally Corneal precipitates or fibrinous uveitis - Occasionally bilateral "lumpy" renomegaly	(1) Mature neutrophilia (2) Hyperglobulinemia with polyclonal gammopathy (3) FIP titer undependable & nonspecific	(1) Pyogranulomatous (2) Straw-colored, viscous, rarely chylous (3) Cytology: moderate numbers of neutrophils, RBC, plasma cells, macrophages, lymphocytes, granular background	(1) Thoracocentesis (2) Supportive	Grave

Table 3. Continued.

Intravenous fluid overload	Sudden onset of dyspnea in cats being Rx with IV fluids; muffled chest sounds; occasionally edema	(1) Possible occult Cardiomyopathy made apparent with fluid overload (2) Possible coexisting anemia or hypoalbuminemia predisposing to fluid overload (3) Sometimes purely iatrogenic from over-zealous treatment	(1) Pure transudate (2) Clear (3) Almost acellular on cytology	(1) Thoracocentesis (2) Judicious use Of diuretics (3) Give plasma or whole blood transfusion for hypoalbuminemia & anemia, respectively	Good if no serious underlying cause is present
Acute trauma or bleeding disorders	- Dyspnea - Variable muffled chest sounds - Other signs of trauma or sites or hemorrhage	(1) Trauma- variable (2) Coagulopathy – abnormalbleeding test parameters; ie, prolonged PT, PTT, low platelet count (2) Radiographs in trauma often denote fractured ribs & pulmonary contusion pattern (3) Exposure to anticoagulant drugs or poisons	(1) Blood red; defibrinated (2) RBC & WBC proportions similar to blood	Trauma - depending on injury; usually conservative rest in the absence of other serious problems. Coagulopathy - (a) whole blood transfusion if severe (b) cryoprecipitates (c) vitamin K_1, for warfarin intox.	Usually good
True chylothorax	- Dyspnea - Muffled chest sounds - Occasional cough	(1) Possible history of prior chest trauma (2) Occasional lymphopenia (3) Other causes include heart failure, heart worms, neoplasia	(1) Milky white (2) Cytology: normal lymphocytes, small # of RBC, smudge cells (3) Orange staining Chylomicrons with Sudan III (4) Elevated triglycerides	Surgical ligation of thoracic duct & anomalous lymphatics	Fair to guarded
Thoracic carcinomas or sarcomas	- Dyspnea - Muffled chest sounds - Possible location of extrathoracic source of neoplasia	(1) Radiographs: demonstration of neoplasm (2) Tissue biopsy confirmation if extrathoracic source is accessible	(1) Usually serosanguineous (2) Obstructive or inflammatory (3) Cytology: RBC, mononuclear cells, mesothelial cells, anaplastic cells (variable presence)	(1) Thoracocentesis (2) Surgical removal if there is solitary mass (3) Chemotherapy	Guarded to grave

FLUID THERAPY FOR CRITICALLY ILL DOGS AND CATS

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Fluid therapy in clinical medicine is used to fulfill the following objectives: (1) to replace dehydration deficits, (2) to maintain normal hydration, (3) to replace essential electrolytes and nutrients, and (4) to serve as a vehicle for the infusions of certain intravenous medications. Except for the urgency of treatment, the same objectives apply in the critically ill animal. The methods for providing fluids often influence the eventual outcome of the case. The clinician and staff, therefore, should familiarize themselves with the pathophysiology of the diseases they are treating and how these conditions relate to the various types of fluids that are available for general use.

FLUID VOLUME REPLACEMENT

The animal requires fluids for (1) rehydration, (2) maintenance, (3) replacement of insensible loss volumes, and (4) replacement of ongoing loss volumes. Clinically, the amount of fluid needed to correct dehydration deficits can be assessed from the degree of skin turgor, capillary refill time, and pulse rate and quality. The degree of dehydration ranges from 5% to 12%. Skin turgor assessment can sometimes be misleading in the obese animal, because adipose tissue replaces subcutaneous interstitial water and maintains elasticity despite negative water balance. Also, old, cachectic patients that have lost skin resiliency may give a false impression of marked dehydration. To clarify the diagnosis in such questionable situations, clinicians can check for the elevated packed red cell volume and plasma total solids that accompany the hemoconcentration caused by volume depletion. Discretion should be used when interpreting these clinicopathologic parameters, because lab values in an anemic animal with concomitant hypoproteinemia may seem normal even if the animal is dehydrated.

The volume of fluid needed to correct dehydration is calculated from either of the following formulas:

- Volume (mL) of fluid needed = % dehydration x body weight (lb) x 500
- Volume (mL) of fluid needed = % dehydration x body weight (kg) x 1000

The maintenance volume is that amount normally required in a 24-hour period by a well-hydrated patient. Taking insensible fluid loss into consideration, which amounts to 13 to 20 mL/kg/day, the 24-hour maintenance volume for a dog or cat whose urine output is normal is approximately 50 to 60 mL/kg (25 to 30 mL/lb) per day. The total 24-hour fluid requirement for the dehydrated animal is the sum of maintenance volume and volume required to correct dehydration.

The initial rate and route of fluid delivery depend on the patient's status. Mildly to moderately dehydrated small dogs and cats that require short-term fluid treatment can be adequately managed with subcutaneous fluids.

Any severely (>10%) dehydrated patient should initially receive fluids intravenously. Because of the accompanying vasocollapse, medications injected subcutaneously may not be adequately absorbed into the systemic circulation. For the mildly to moderately hypovolemic patient, it is recommended that one fourth to one half of the estimated dehydration deficit be replaced over the first 2 to 4 hours with the remaining dehydration deficit and maintenance isotonic volumes administered over the subsequent 20- to 22-hour period. The amount of subsequent fluid infusion will depend on the patient's response to treatment.

Exceptions to the recommended maintenance doses of fluids occur under the following circumstances:

- **Oliguria and anuria.** After dehydration deficits are replaced, the patient's maintenance needs depend on urinary output, which should be estimated or quantitated. Providing full normal maintenance fluid volumes to oliguric and anuric patients can lead to fatal pulmonary edema or pleural effusion because of iatrogenic intravascular fluid overload. Specific treatment for low output renal failure is provided in the next section.
- **Polyuria.** Polyuric animals require fluid volumes in ...excess of normal maintenance needs. Failure to provide these volumes can result in a sustained negative water balance if the patient is unable to drink. The maintenance needs for polyuria consist of exact urinary losses plus insensible and ongoing losses. Assurance of adequate treatment is made by weighing the patient each day as well as by assessing the physical and laboratory parameters for hydration. An acute loss of 1 kg of body weight suggests a 1 L fluid deficit.
- **Rapid internal shifts of fluid**, which can occur in pancreatitis, extensive burns, enteritis, and gastrointestinal obstructions. In these conditions, the fluid needs of the patient will exceed the usual maintenance volumes by as much as three times.

The assessment of the animal's fluid requirements must always be made within the pathophysiologic context.

ANEMIA

Intravenous fluids are sometimes used excessively in the anemic patient when the decrease in red blood cell mass is misinterpreted as total blood volume depletion, when in fact the plasma volume might even be expanded. To compensate for decreased tissue oxygen delivery, the heart rate increases, and if these patients are subjected to large fluid volumes over a short period of time, pulmonary edema can occur.

Anemic cats in particular are susceptible to intravenous overload from crystalloid infusions. The dehydration deficit and maintenance fluid volumes should be gradually replaced over a 24-hour period with an isotonic crystalloid solution, while fresh whole blood is used to replace the red blood cells. The volume of whole blood infused should be considered when calculating the volume of crystalloid for infusion.

EXTRACELLULAR FLUID VOLUME EXCESS

This condition is associated with an increase in total body salt and water and occurs in a variety of clinical settings including congestive heart failure, glomerulopathies, liver fibrosis, and protein-losing enteropathy. These conditions are associated with a decrease in "effective arterial volume," which stimulates the renin-angiotensin-aldosterone cycle and the release of antidiuretic hormones to promote renal salt and water retention, respectively. Because of increased venous pressure from heart failure and cirrhosis or because of decreased plasma oncotic pressure associated with hypoalbuminemia, the retained salt and water move into the interstitial and other body spaces, causing edema, ascites, or pleural effusion. Hypervolemia amounting to 20% to 30% in water excess can cause pulmonary edema.

Patients with any of these conditions are extremely sensitive to intravenous overload with crystalloid solutions. Treatment should be directed toward improving the underlying primary pathologic process. Fresh or fresh frozen plasma should be used to volume expand animals with hypoalbuminemia, although in glomerulopathies and protein-losing enteropathy (PLE), beneficial effects are usually temporary at best because of continued protein losses especially with PLE.

Heart failure patients receiving intravenous fluids should be closely observed for weight gain and respiratory distress caused by intravascular fluid overload. A rapid respiratory rate will often be the earliest sign of overload therefore calling for close patient observation. Under optimal conditions, monitoring of central venous and pulmonary wedge pressures is helpful for avoiding this potentially fatal complication. The reader is referred to other sources for details regarding these techniques.

When parenteral fluid therapy is indicated in the cardiac patient, solutions containing little or no sodium are given after dehydration and hypovolemia are corrected with isotonic solutions. Either 0.45% saline or D-5-W can be used. Efforts should be made to avoid hypokalemia by adding potassium chloride solution to the fluids at a dose of 7 to 10 mEq/250 mL. Periodic monitoring of serum electrolytes is necessary for accurate treatment adjustments.

HYPOVOLEMIC SHOCK

The loss of 30% to 40% of intravascular volume will cause severe hypovolemia and hypotension. Cardiac arrest occurs when 50% to 60% of blood volume is lost.

Isotonic crystalloid solutions [saline 0.9% (NS), acetated Ringer's or lactated Ringer's solution (LRS)] are the most commonly used replacement fluids because they are usually effective, readily available, easily administered, and relatively inexpensive. Severely hypotensive patients might require at least one whole blood volume of replacement fluids during the first hour of treatment. Initial rapid infusion for dogs should be 20 to 40 mL/kg IV (one half this amount for cats) for 15 minutes, followed by 60 mL/kg (dogs) or 20 mL/kg (cats) administered over one hour. This loading volume is followed by administration of maintenance fluids at a rate of 10 to 12 mL/kg/hr for dogs and 5 to 6 mL/kg/hr for cats. The patient's heart and respiratory rates and urine volume are monitored every 15 minutes during vascular volume resuscitation. Any signs of fluid overload necessitate prompt decreases in fluid delivery and consideration of diuretic therapy. Optimally, central venous or pulmonary arterial wedge pressure determinations should be used to monitor the patient's hemodynamic status.

This particular fluid regimen is especially useful for treating dogs and cats with trauma-induced peracute blood loss. It has also been proved efficacious for treating other conditions in which plasma volume is depleted rapidly, such as the canine hemorrhagic gastroenteritis (HGE) syndrome. After volume loading an HGE patient with crystalloid solution, the plasma proteins will decrease substantially. In most cases this will begin to correct itself after the first 24-hour period of treatment.

Vigorous fluid administration can cause significant problems: a rapid increase in hydrostatic pressure, dislodgement of previously formed hemostatic plugs, reduced blood viscosity, and dilution of oxygen carrying capacity and coagulation factors.

In a setting of traumatic hemorrhage restoring the systolic blood pressure to no more than 60 mmHg can help avoid dislodgement of any clots that have formed.

Any coexisting pulmonary contusions, cardiogenic shock, and hypoproteinemia requires cautious delivery of IV crystalloid solutions.

VOMITING

Vomiting is the principle sign of gastric disease, but it can also accompany disorders of the small or large bowel, liver, and pancreas, as well as disorders occurring outside of the digestive system. Vomiting can deplete the body of a substantial volume of fluids and electrolytes. The specific types of electrolyte deficiencies and acid-base abnormalities depend on the location of the primary disorder. Vomiting caused by pyloric outflow obstructions typically can lead to dehydration, metabolic alkalosis, hypochloremia, hypokalemia, and hyponatremia. NS supplemented with potassium chloride (3 to 10 mEq/kg_{BW} every 24 hours) is the fluid of choice.

Fluid losses through vomiting associated with systemic illness or intestinal disease are best replaced with lactated or acetated Ringer's solutions. The patient's serum electrolyte status should be monitored and corrected when indicated.

GASTRIC DILATATION-VOLVULUS (GDV)

The GDV complex causes hypovolemic shock as well as gastric sequestration of fluids and electrolytes.

Although the hypovolemia can cause tissue hypoxia and eventually metabolic acidosis, there are several instances in which the gastric hydrogen and chloride ion sequestration can offset the acidosis and perhaps even cause a metabolic alkalosis. Although most dogs with GDV are initially volume resuscitated with LRS, their acid-base parameters should be monitored if possible in order to detect any need for a change in fluid type.

OLIGURIC AND ANURIC RENAL FAILURE

The urine output of all critically ill patients should be monitored, especially during periods of intensive fluid therapy. Fortunately, many oliguric patients will begin producing urine after they receive one half of their estimated dehydration deficit values during the first one to two hours of treatment. If urine production is inadequate, the following protocol is recommended:

- Insert an indwelling urethral catheter and empty the urinary bladder of any residual urine.
- Administer the calculated dehydration deficit fluid volume over the first two to four hours of treatment.
- Once rehydration has occurred, administer furosemide (4 mg/kg IV push) and/or mannitol (0.5 g/kg IV) over a 10-minute period.
- If no urine flow occurs, readminister furosemide (8 mg/kg IV push) or administer dopamine (1 to 2 µg/kg/min IV).
- If oliguria or anuria persists, the amount of fluids infused per day will consist of the sum of the measured urine output, the insensible water loss (13–20 mL/kg/day), and the extra losses caused by vomiting or diarrhea. Peritoneal dialysis will be required to rid the body of uremic toxins.

Plasma volume expansion should be accomplished with LRS or NS; the latter is preferred if hyponatremia is present. Maintenance fluids can initially consist of Ringer's lactate or acetate but can eventually be reduced in concentration to one-half strength in the absence of any renal sodium-losing disorder.

DIARRHEA

The fluid deficit from massive diarrhea can be efficiently corrected with LRS because it resembles the type of fluid lost, is readily available, and provides uniformly good results. In markedly hypotensive patients, the intravenous fluids should be given as described previously (see Hypovolemic Shock).

HYPEROSMOLAR CONDITIONS

The common causes of extreme hyperosmolality in the dog and cat include hyperosmolar nonketotic diabetes mellitus, hypernatremia associated with water deprivation in diabetes insipidus patients, and essential hypernatremia (in dogs). In hyperosmolar diabetes, dehydration is easily detectable through skin turgor evaluation; in the latter two conditions, the interstitial water is often retained because of a shift of fluid from the intracellular space, thereby allowing for normal skin turgor. Eventually, however, the subcutaneous water will become depleted. In each of these conditions, hypovolemia can be life-threatening.

It would seem logical that a hypotonic solution such as D-5-W (252 mOsm/L) would be the fluid of choice; however, this solution rapidly exits from the intravascular space (two thirds of the infused volume exits within the first hour), and thereby does little to expand the intravascular fluid space. The preferred initial fluid, therefore, is NS because of its isotonicity, its tendency to persist within the intravascular space for a reasonable length of time, and its hypotonicity relative to the patient's hyperosmolar plasma. After adequate plasma space resuscitation, the infusion can be changed to 0.45% saline with or without 2.5% dextrose added.

In marked hypernatremia (serum Na^+ > 165 mEq/L), the goal of treatment is reduction of the serum sodium level by 0.5 to 1.0 mEq/L per hour, replenishing one half of the water deficit in 12 to 24 hours and the remainder in another 24 hours. This gradual water replacement will prevent cerebral edema and death, which can be caused by too rapid correction of the serum sodium level.

HYPOTONIC DISORDERS

A hypotonic disorder is one in which the serum osmolality and sodium levels are reduced in parallel. Clinically significant hyponatremia is most often due to an inability to excrete a maximally dilute urine.

The goal of treatment in hyponatremia is to correct body water osmolality and restore cell volume by raising the sodium-to-water ratio of extracellular fluid. Acute hyponatremia occurs when the decline in serum sodium exceeds 0.5 mEq/L/hr. When levels fall below 120 mEq/L, with associated brain dysfunction, the condition should be treated immediately. Hypertonic saline (3% or 5% is administered at a rate of at least 1 mEq/L/hr to replace sodium.

Chronic hyponatremia is more common than the acute form and occurs when the rate of decline is less than 0.5 mEq/L/hr. Slow correction, essential for preventing central pontine myelinosis, is accomplished by administering NS and furosemide at a rate of less than 0.5 mEq/L/hr.

HYPERCALCEMIA

Many patients with hypercalcemia are volume depleted. Initially, NS should be infused to normalize intravascular volume. Because the renal excretions of sodium and calcium are linked, a forced saline diuresis using furosemide and isotonic saline will accelerate calciuresis. Close monitoring of serum electrolyte levels, especially potassium, is essential to detect and correct possible hypokalemia. All patients receiving rapid saline diuresis should be monitored for signs of intravascular fluid overload.

PULMONARY CONTUSIONS

Patients with this lesion are predisposed to capillary leakage and fluid accumulation in their lungs. Excessive IV fluid flow rates can definitely cause this problem. Judicious use of hypertonic saline or hypertonic saline combined with Dextran 70 will help to facilitate intravascular volume expansion while avoiding pulmonary overload.

Head Trauma

Fluid therapy is aimed at maintaining cerebral perfusion pressure while decreasing intracranial pressure using mannitol at 1 g/kg IV over 15 minutes. Current recommendations for systemic resuscitation call for combined hypertonic saline and Dextran 70 given at 2 to 4 mL/kg over 5 to 10 minutes. In head trauma patients who are not hypotensive, you can give hypertonic saline at 4 mL/kg over 30 minutes.

PRACTICAL PEARLS FROM THE EMERGENCY ROOM

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After 37 years of practice, a clinician can come to the clear conclusion that the practice of medicine consists of a fine blend of both the art and the science. Perhaps it might be rather bold to state that at times the value of the art might even surpass that of the science, even in the academic environment. The main objective of this collection of thoughts is to share some of the lessons that I have learned over the years with the hope that you will walk away with a few PEARLS that will benefit your sick patients. For the sake of simplicity, each pearl has been categorized according to organ system and will be presented in short and simple phrases. First, to share a bit of philosophy:

THE ART OF DIAGNOSIS

- To make the correct diagnosis, we need the right choices.
- To consider the right choices, we need the right information.
- To obtain the right information, we need to ask the right questions.
- Asking the right questions is the hallmark of clinical expertise.

—R. Kreisburg, MD

PATIENT EVALUATION

- Pallor can be caused by hypoxia, shock, anemia, and an epinephrine injection.
- Anemic pallor plus icterus causes a yellow hue.
- Pink mucous membranes plus icterus causes a more orange color.
- Massive generalized lymphadenopathy usually means lymphoma.
- If it looks, smells, and tastes (?) like pus, then it must be pus.
- Chest plus abdominal fluid accumulation commonly depicts a bad disease. Common causes: neoplasia, heart failure, diffuse inflammation, hypoproteinemia.
- Septic shock – Hypotension, hypothermia, thrombocytopenia.
- Skin turgor difficult to assess with cachexia and obesity.
- Sudden facial swelling, hemorrhagic oral mucosa, subdued mentation – Think Eastern diamondback rattlesnake envenomation (in Florida).
- Various causes of hyperventilation – Cardiorespiratory, pyrexia, brain disease, Cushing's, metabolic acidosis, anxiety, pain, shock, anemia.
- Fever plus immune-mediated disease – Appetite can persist.
- Fever plus sepsis – Anorexia.
- Nasal crustiness, scleral injection, muddy mucous membranes – Think uremia.
- On palpation: "Touch but don't squeeze the Charmin."
- Take the patient out of the cage and look at it!
- If something just "ain't" right – Think Neuro.
- Look under that tongue in any vomiting cat (and dog).
- Watch those rear legs for the earliest sign of weakness.
- THE BIG 6: PCV and TP, BUN, Glucose, UA, Chest/Abdominal radiographs.
- After therapeutic pericentesis, go back and repeat abdominal palpation so you don't pass the mass.
- Have you been palpating each mammary gland?
- A lump is a lump until you stick it.
- It's all in the history.
- Don't just look at it (a lump) – stick it!
- Heatstroke > 109.4°F – look out DIC.

UROGENITAL

- Rule out pyo in any sick intact female.
- Never let the sun set on a pyo (Garvey, M).
- Murky urine can be caused by: pus, chyle, crystals.
- Bilateral renomegaly means very serious disease: lymphoma, hydronephrosis, pyonephrosis, granuloma, inflammation, subcapsular edema, polycystic.
- Cats: 1 big kidney plus 1 small kidney can mean 1 fibrotic and 1 compensatory hypertrophic.
- Hematuria without stranguria – consider coagulopathy or renal bleed; however a...
- Recent renal bleed plus clots – can cause stranguria.
- Male dog plus stranguria – must radiograph to rule out obstructive uropathy.
- Cessation of polyuria in sick patient – consider oliguria/anuria – a bad sign.
- Oliguric renal failure – hyperkalemia common.
- High output chronic renal failure – normo- or hypokalemia common.
- Emphysematous cystitis – R/O diabetes mellitus.
- PD plus PU plus isosthenuria – consider chronic renal disease, even with normal BUN and creatinine, but watch out for Cushing's.
- Careful on "cysto" with pyometra, look before your stick!
- Prostate trends: carcinoma – asymmetrical, hard, mid or caudal pelvis; BPH – symmetrical, firm, anterior displacement.
- Empty urine line: anuria, recent emptying, obstruction.
- Always assess urine SG before starting fluid Rx.
- BPH: Passive penile bleed, normal urination, normal dog.
- Detection of urethral pathology in female dog, do rectal exam.
- Prostate inflammation → "prostatic shuffle".
- For oliguria, try dopamine at 3–5 μg/kg/min.

FLUIDS AND ELECTROLYTES

- SQ fluid administration – isotonic, 18- gauge needle, gravity flow
- Metabolic alkalosis plus hypokalemia common with upper GI obstructions.
- 0.9% NaCl plus KCl – Best for upper GI obstructions.
- TCO_2 >40 mEq/L is always metabolic alkalosis (usually with hypokalemia).
- TCO_2 < 10 mEq/L usually means severe metabolic acidosis.
- Potassium penicillin contains 1.7 mEq K+/million units – take heed when bolusing.
- Rx hypocalcemia when IV not an option: add 2.5 mL/kg 10% calcium gluconate to 150 mL 0.9% NaCl – give SQ Bid (for adult sized cat).
- When giving SQ fluids avoid hypokalemia – add 3.5 mEq/KCl/150 mL LRS – give SQ (for adult sized cat).
- All IV maintenance fluids should contain 7–10 mEq/KCl/250 mL; exceptions oliguria and untreated Addisonian.
- To make up 2.5% dextrose solution increments, add 12.5 mL D-50-W to 250 mL of fluids.
- Rehydrate before inducing diuresis; check urine SG first.
- Volume load with isotonic crystalloid.
- Intraosseous cannulas can be life saving.

GASTROINTESTINAL

- GI obstructions – Main sign is vomiting.
- Acute excruciating abdominal pain (like never before seen!) – Consider bowel infarction and intestinal volvulus.
- Causes of coffee ground vomitus – Gastric ulcers (primary/secondary), uremic gastritis.
- Melena causes – Upper GI lesion, thrombocytopenia.
- Occult blood loss – Think GI.
- Melena detection – "Let your finger do the walking".
- Black stools – Upper GI bleed, thrombocytopenia, swallowing blood, "Pepto," iron, charcoal.
- Elevated BUN plus normal creatinine – Consider upper GI bleed, especially if kidney can concentrate urine.
- Bile in vomitus signifies pyloric patency.
- The lower the obstruction, the more feculent the vomitus.
- Sudden mental depression 2–3 days post enterotomy – rule out dehiscence and sepsis.
- Never let the sun set on a linear foreign body intestinal obstruction.
- Diffuse inflammatory bowel disease can often be diagnosed with distal colon biopsy.
- Sepsis can cause cholangiostasis.
- Gas in the gallbladder is a bad and a surgical disease.
- Bilirubinuria without hemolysis in cats signifies liver disease.
- J-tube feeding for managing the prolonged period of NPO in pancreatitis can be beneficial.
- Look for pancreatic pathology when the right kidney is easily visible on a radiograph.

CARDIORESPIRATORY

- Many die without ever showing open mouth breathing.
- Watch for the exaggerated abdominal component.
- Cardiomegaly does not always cause tall EKG complexes.
- A standing lead 2 EKG is satisfactory for rate, rhythm, and interval measurements.
- Do not use beta blockers until pulmonary edema resolves.
- Muffled chest sounds: fluid, mass, air, obesity, deep chested, "plugged ears."
- Diffuse muffling – Usually chest fluid.
- Dorsal muffling – Air or mass in chest.
- Coughing cats – Allergic bronchitis, flukes, lung worms, heartworms, hair or foreign body in trachea, tumor.
- Sudden onset diffuse pulmonary infiltrates, think ARDS.
- Cats with heart disease rarely cough.
- Bacterial pneumonia plus leukopenia (bone marrow associated) – causes minimal radiographic infiltrates.
- Heartworm treated dog at discharge: dispense prednisone and furosemide for the earliest signs of PTE.
- Echocardiogram for diagnosing vegetative endocarditis.
- 3–5 mg (total) ketamine IV for a dyspneic cat can allow "survival" radiographs.
- Remember – Good side UP when radiographing dyspneic patient.
- Digoxin intoxication can cause any cardiac arrhythmia.
- Aspiration pneumonia can be worse when H_2- or H^+ blockers are used due to altered GI microflora.

NEOPLASIA

- Cutaneous mast cell tumors can mimic any type of skin growth.
- Assume any firm mammary nodule as carcinoma until proven otherwise.
- Mammary tumors – Don't stick it – cut it.
- Don't miss lymphangitic inflammatory mammary carcinoma.
- Nasal disease can do anything.
- Copious mucoid nasal discharge – Think nasal adenoCA.
- Try gastric biopsy forceps for nasal biopsy.
- Closed mouth nasal cavity radiographs are useless.
- Cancer can cause elevated T. WBC and fever.

DRUGS

- Observe for drug interactions.

- Do not use theophylline with Cipro – causes theophylline OD.
- Best avoid IV route for thiamine (better IM) and Vitamin K1 (better SQ).
- Rehydrate prior to using aminoglycosides.
- Prednisone for craniomandibular osteopathy.
- Cimetidine enhances metronidazole-induced neurotoxicity.
- Aspiration pneumonia worse when H_2-blockers in use.
- Panmycin can cause fever in cats.
- Follow all oral doxycycline with water to swallow.

HEMATOLOGY

- Unclotted blood in clot tube – Consider coagulopathy.
- Massive splenomegaly – Splenic torsion, lymphoma, myeloproliferative or mast cell splenic neoplastic infiltrate.
- Thrombocytopenia plus anemia – Causes pale petechia!
- Fleas plus thrombocytopenia – Cause "lots of" lumbosacral petechia.
- Low WBCs, low RBCs, low platelets – Rule out bone marrow suppression.
- Fulminant hemolysis – Anemia, Hb-emia, Hb-uria, weakness, depression, +/- vomiting.
- Bone marrow-derived leukopenic animals don't make pus!
- Keep IMHA and ITP patients on long-term q2d maintenance prednisone for 9–12 months.
- Try Danazol (Danocrine) with prednisone for refractory IMHA and ITP.
- Observe for autoagglutination and spherocytes in IMHA.
- Newly acquired bleeding, think warfarin intoxication.
- A normal bleeding time ensures adequate platelet hemostasis, a normal platelet count does not.

ENDOCRINE

- Hypercholesterolemia plus elevated CK – Rule out hypothyroidism.
- U-100 syringe (or TB) must be used for U-100 insulin.
- Do not forget K+ when treating DKA.
- Oliguric diabetics have marked hyper-glycemia.
- Glycosuria can occur with diabetes, proximal renal tubular disease, stress, IV dextrose.
- Marked hyperglycemia with minimal glycosuria - consider oliguria/anuria.
- Morning marked glycosuria and afternoon diminished glycosuria – Typifies transient insulin response (need split dose).
- Can use soiled litter to detect glycosuria.
- Hyperglycemia can sometimes be detected in tears.
- The "Accucheck" blood glucose meter is nice (and inexpensive).
- Assess the eclampsia dog for hypoglycemia.
- Try mannitol or hypertonic saline for severe hypoglycemic encephalopathy.
- When Florinef does not work well, use DOCP and prednisone.
- The hypocalcemic cat has not read the book.
- Keep an eye out for the atypical Addisonian.

NEUROLOGY

- Rapid onset LMN paralysis, think – Ticks, organophosphate, botulism, polyradiculoneuropathy, metronidazole, coral snake.
- Cats with dilated pupils and blank stare – Think thiamine.
- Coma – Diffuse cerebral, stem, but don't forget metabolic.

INTOXICATION

- Ethylene glycol fluoresces.
- DMSA (dimercaptosuccinic acid - Succimer; McNeil) – An oral Rx for lead poisoning.
- Unexplainable radiodense particles in the bowel - think lead.
- 4-methylpyrazole 5% for antifreeze intoxication; avoids hangovers.
- Newer anticoagulant rodenticides – Treat for 4–6 weeks.
- Newly acquired bleeding – Think warfarin OD.

PATIENT MANAGEMENT

- Old dogs are poorly tolerant to tranquilization.
- Avoid sedating acutely ill patients unless absolutely necessary.
- Don't sedate at the end of day.
- Increased spontaneity might pre-empt death.
- Heparinized syringe might contain as much as 200 units heparin – too much for puppies and kittens.
- Traumatic ear flush can cause inner ear and vestibular disease.
- Cats hate atropine drops (use ointment instead).
- Some pathologic bladders can leak after cystocentesis.
- Do not forget THIAMINE in cats.
- Glycerine suppositories for patients with pelvic fractures will be most appreciated!
- Three (3) mg (total dose) ketamine IV – Can adequately restrain the sick cat with urethral obstruction.
- Careful with SQ fluids – dogs are not cats and they like to slough!
- Manual expression of a male dog's bladder is hazardous to its health – It can rupture.
- SQ fluid administration – Stay behind the scapula and in front of the wing of the ilium. Use 18-gauge needle and 50 mL/site (adult cat).
- Don't forget glucose for the babies.
- Imipenem for life threatening infections.
- A clean cat is a happy cat.
- No Fleet enemas for obstipation, unless you want to treat a good case of hypocalcemia.

- When is the last time you hugged your patients?
- A dynamic duo: Good science and experience.
- Heat lamp and rubbing alcohol = one HOT dog.
- Nothing is routine.
- If client can not afford a "Cadillac," there is nothing wrong with a "Chevy."
- Body bandage in cats cause pseudoparalysis.
- Rapid abdominocentesis is effective and safe for chronic ascites, except when it is caused by chronic liver disease whereby simultaneous IV plasma or albumin infusion is recommended.
- Best avoid IV B_1 and K_1 – Give SQ or IM.
- Never kill 'em based on cytology results.

CARING FOR THE CRITICALY ILL ICTERIC CAT

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The detection of icterus in the dog and cat poses a diagnostic challenge to the veterinary practitioner. Because icterus has several very different etiologies, it is best to pursue the cause initially by attempting to answer the question: Is the icterus due to a prehepatic, hepatic, or posthepatic disorder?

PREHEPATIC

This particular cause of icterus accompanies a hemolytic condition that allows for the accumulation of unconjugated bilirubin. Some of the causes of hemolysis in the cat are hemobartonellosis (*Mycoplasma haemofelis*), adverse drug reactions (acetaminophen, methylene blue), autoimmune hemolytic anemia (often FeLV positive), transfusion reactions, and hemolytic disease of the newborn. The history and the physical examination findings will often help to differentiate the causes of prehepatic icterus.

The laboratory findings will support the prehepatic origin of icterus based on the presence of a regenerative anemia and other features depending on the particular etiology as shown with RBC Heinz body formation with certain drug toxicities such as acetaminophen and methylene blue. Hemobartonella (Mycoplasma) should be searched for. In the cat, it should be noted that many of the positive cases of *Mycoplasma haemofelis* or the Coombs positive hemolytic anemia are also FeLV positive. Hemoglobinuria and hemoglobinemia usually accompany an intravascular hemolysis.

Treatment depends on the particular etiology. Acceptable cross-matched blood should be given if the patient is weak and depressed or if it has a packed cell volume of < 15%. Discontinuing any causative offending drug should be immediate if the hemolysis is drug related. In the case of IMHA, immunosuppressive doses of glucocorticoid (prednisone 1–2 mg/kg once or twice daily) are begun immediately. Other immunosuppressive or immune modifying drugs can be given depending on the patient's status and its initial response to treatment. Persistently FeLV positive cats usually have a very guarded to grave prognosis.

HEPATIC

This includes both primary and secondary causes of hepatic disease. Only the primary and more common types will be discussed here.

Feline Primary Idiopathic Hepatic Lipidosis

This is a common syndrome in the indoor cat. The history often provides a stressful event that triggered the inappetence. Anorexia and its effects on protein and lipid metabolism may play an important pathogenetic role. Abnormal triglyceride metabolism is thought to reflect other derangements in hepatocyte functions that contribute to hepatic failure.

There is no age, breed or sex predisposition, but obesity is considered a contributing factor. The common clinical features include anorexia of several days to weeks duration, lethargy, and depression. Intermittent vomiting and diarrhea can also occur. The physical examination often detects a palpably enlarged smooth surfaced liver, icterus, varying degrees of dehydration, and evidence of weight loss.

The clinical pathologic abnormalities include a nonregenerative anemia and elevated serum transaminase, alkaline phosphatase, and bilirubin levels. Bilirubinuria is common and indicative of liver disease in the cat in the absence of hemolysis. Coagulation abnormalities occur with the advanced form of disease. The presence of hepatic fat deposits found on cytology specimens obtained by fine needle aspiration or histopathologically on a liver biopsy specimen are confirmative.

Treatment for idiopathic hepatic lipidosis entails restoring hydration along with the provision of nutritionally balanced feedings. The latter can be accomplished with "finger feeding" baby food (without onion powder) or more efficiently through nasogastric, pharyngostomy, or gastrostomy tubes. Tube feeding will allow for the delivery of a more nutritionally balanced diet.

Ursodeoxycholic acid (Ursodiol) is a choleretic agent that increases bile flow and decreases bile toxicity. It is dosed at 10–15 mg/kg once daily orally.

S-Adenosylmethionine (SAMe) is a product that increases hepatic glutathione levels thereby providing a protective antioxidant effort for the liver. The dose is 18 mg/kg once daily orally.

Milk thistle also has protective effects on the liver. The compound containing silymarin extract is dosed at 0.25 mL q8–12h orally.

B vitamins are generally administered. This author prefers not to use benzodiazepine tranquilizers to stimulate the appetite because of sedative side effects and their potential for hepatotoxicity in the cat.

The prognosis is fair to guarded depending on whether or not the anorexia disappears and the appetite returns. Predisposing psychological stressors might be difficult to reverse.

Hepatic lipidosis in the dog is generally a secondary disease associated with diabetic ketoacidosis. It will resolve once the primary disorder is cured.

Cholangiohepatitis

This is an inflammatory disorder of the hepatobiliary tree. In the cat it has two main types: 1) suppurative cholangitis/cholangiohepatitis and 2) nonsuppurative cholangiohepatitis. Advanced inflammatory disease can progress to cirrhosis. These syndromes can be associated with other conditions such as duodenitis, pancreatitis, and cholecystitis. In the tropics, cholangiohepatitis can be caused by the liver fluke, *Platynosum concinnum*. Cholangiohepatitis in the cat can occur with cholecystitis with the latter often becoming a surgical disorder when it becomes emphysematous or if it is associated with biliary outflow obstruction.

The clinical signs include varying degrees of anorexia, weight loss, dehydration, vomiting, diarrhea, hepatomegaly, and jaundice. Fever is sometimes present especially in the cat with suppurative cholangiohepatitis. Anterior right-sided abdominal discomfort might be evident on palpation. The clinical pathologic features include elevated serum transaminases, alkaline phosphatase, and bilirubin levels and bilirubinuria. A neutrophilia is common with the suppurative type. Eosinophilia is occasionally present with fluke infections in the cat. A liver biopsy is necessary for a definitive diagnosis. Some advocate ultrasound guided percutaneous gall bladder aspiration for culture and cytology, but this procedure might cause leakage and bile peritonitis.

Fluid therapy and B vitamins are important for both types of cholangiohepatitis. Vitamin K_1 should be given when there is obstruction to bile flow. Antibiotics are strongly recommended for the suppurative form; those commonly used include those effective against gram negative bacteria. SAMe and milk thistle are also used as liver support drugs.

For nonsuppurative cholangiohepatitis in the cat, prednisone is recommended at a daily dose 2.2 mg/kg for 1 to 2 weeks and then slowly tapered to an alternate day regimen over a 4- to 6-week period.

Feline liver flukes are treated with praziquantel at 20 mg/kg once daily for 3 consecutive days. Fenbendazole at 50 mg/kg PO can also be given for 5 consecutive days. The prognosis is fair to good if the condition is treated before biliary fibrosis becomes established.

Cholestasis

Cholestatic hepatopathy is characterized by bile stasis within the canaliculi. It can occur with cholangitis, cholangiohepatitis, or it can be due to adverse drug reactions on the liver. Other causes include various enterotoxins, sepsis, and certain inflammatory disorders such as acute pancreatitis. These conditions are managed medically along with the discontinuation of any predisposing medications, herbs, or other hepatotoxins and the treatment of the primary underlying disorder. Liver supportive measures can include the administration of ursodiol, SAMe, milk thistle, and adequate nutrition and vitamins.

POSTHEPATIC

The posthepatic causes of jaundice in the cat include those disorders that cause common bile duct obstruction.

The clinical pathological features of this group of disorders include remarkably elevated serum alkaline phosphatase, cholesterol, and bilirubin levels. Serum transaminase levels will vary from mild to moderately elevated. The hemogram is seldom contributory, except for prolonged coagulation times due to the inactive vitamin K dependent factors II, VII, IX, and X. Parenteral vitamin K_1 treatment is recommended.

Radiographs and abdominal ultrasound examinations might suggest masses or markedly dilated bile ducts. Surgical exploratory is essential for an absolute diagnosis and the determination of the treatment plan and prognosis.

CRITICAL CARE FOR THE CAT IN LIVER FAILURE

The main concerns in treating the cat with severe liver disease are nutrition, fluid and electrolyte balance, hepatic encephalopathy, and coagulation disorders.

Nutrition

Oral feeding or feeding with the assistance of a pharyngostomy, esophagostomy or gastrostomy tube would be the ideal way to maintain the patient so long as it is not vomiting. In the case of significant vomiting (more than twice/day), parenteral nutrition will have to be instituted. It is essential to provide an adequate caloric base to allow the cat to be maintained in an anabolic state. The required amount of calories needed per day (RER) can be computed using the formula where

$$\text{RER} = 70 \times (\text{Body weight in kg})^{0.75} \text{ or}$$
$$\text{RER} = 30 \times (\text{Body weight in kg}) + 70$$

This formula has to be adjusted for catabolism, dietary thermogenesis, and the presence of sepsis. The diet should contain good quality protein and must not be restricted unless hepatic encephalopathy, hyperammonemia, or ammonium biurate crystalluria are present. In the absence of vomiting the protein requirement can be met with most available prescription diets that contain high quality protein, adequate fat and carbohydrate along with adequate vitamins and minerals to meet the cat's daily requirements. If the cat is being tube fed the use of a blender will greatly facilitate its administration. Cats on enteral nutrition will be fed commercially available liquid diets that are made of the right consistency for enteral tube administration. It is important to start such diets slowly so that osmotic diarrhea is avoided.

Sodium intake should be limited to 100 mg/100 kcal energy requirement in hypoalbuminemic cats and in those with ascites. The palatability from such a diet will probably suffer, and in the cat that is already anorectic, tube feeding will probably be essential.

The critically ill cat can very likely become depleted of thiamine and vitamin B_{12}. Thiamine deficiency can cause a severe polioencephalomalacia and is best avoided by providing normal daily needs. Thiamine hydrochloride injection (50–100 mg IM or SQ) should be given in any cat that is showing signs compatible with thiamine deficiency (starry-eyed gaze, fixed mid-position or dilated pupils, ataxia, dementia, and dysequilibrium. Fifty milligrams can be given daily for the next few days followed by normal dietary amounts. Vitamin B_{12} (cobalamine) supplementation might help cats with co-existing pancreatic and small intestinal disease. Blood cobalamine levels can be sent to a commercial laboratory and treatment can be provided with 0.5–1.0 mg of B_{12} IM or SQ every 7 to 21 days.

Vitamin E and Vitamin K_1 are also important nutrients that should be provided for their activity against cellular oxidative injury and coagulation disorders, respectively. A recommended dose for Vitamin E is 10 units/kg/day. Vitamin K_1 is necessary for the facilitation of Factors II, VII, IX and X and is dosed at 0.5 to 1.5 mg/kg sid-bid. **It is important to remember that no vitamin injection should be given by IV push because it will likely cause an anaphylactoid reaction.**

Fluid Therapy

Fluid therapy and meticulous protocols for its administration is an essential part of caring of critical care medicine. Cats are very susceptible to having intravenous fluid overload and should therefore be monitored closely. The special considerations concerning fluid therapy for cats with liver disease include hypovolemia, hypoalbuminemia, blood loss, predisposition to edema and body cavity effusions, and sepsis caused by breaks in sterile procedure. The tendency for sensitivity to fluid overload is because the patient with chronic liver disease can have an active renin-angiotensin-aldosterone system because of the ineffective blood volume they might have. One good way to administer parenteral fluids to such patients is to infuse a slow infusion of both crystalloids and colloids. This can be done with alternating or combined delivery methods. The increased plasma oncotic pressure delivered with this fluid formulation will help restore intravascular Starling's forces to normal by expanding intracellular volume, limiting the requirement of crystalloid, and allowing for a more prolonged lasting effect of the volume expansion efforts. It is recommended that only one third of the normal amount of crystalloid be given if a colloid is given at a dose of 10 mL/kg which is the 24-hour recommendation of Hetastarch for the cat. If either Hetastarch or Dextran 70 is used, it is important to consider their effect on the patient's coagulation status because of their known tendency to antagonize blood clotting which is already a concern in a cat whose liver disease is already compromising hemostasis.

Albumin infusions will benefit the patient with hypoproteinemia and when combined with rapid paracentesis on the ascitic cat, the procedure might avoid being complicated by life-threatening hypovolemia. Although human albumin has been given to several dogs without allergic complications, it might be safer to use plasma from another cat until more is known about the cat's ability to tolerate plasma proteins from other animal species. Any foreign protein carries the threat of anaphylaxis with it thereby calling for much diligence during its administration. All allergic reactions must be met with immediate discontinuation of the plasma or albumin infusion. If necessary, parenteral epinephrine must be given at a dosage of 0.01 mg/kg IM and repeated in 20 minutes if anaphylaxis occurs.

Dextrose-containing solutions should be used whenever the blood glucose concentration cannot be maintained within normal limits of 70 to 125 mg/dL. Hyperglycemia can cause several complications including immune compromise thus predisposing to infection, osmotic diuresis with its attending loss of important electrolytes and water soluble vitamins, and a contributing factor to the formation of respiratory acidosis. However if hypoglycemia is present it should be countered with dextrose administration. Hypoglycemic encephalopathy should be treated immediately with dextrose injection at a dose of 0.5 g/kg, which is met with 1.0 ml of 50% dextrose IV or 2 mL/kg 25% dextrose solutions. Intravenous injections of such hypertonic solutions must not be allowed to extravasate because of the extensive tissue sloughing that can occur.

Treating Anemia

The anemia that occurs with liver disease can be uni- or multifactorial. Blood loss can occur from slow bleeding gastric ulcers, especially if mast cell cancer is the cause of the liver disease. Liver disease alone has been associated with gastric ulcers. Other causes can be the anemia of chronic disease or that due to any co-existing disease such as feline leukemia virus. Lastly and by no means least, iatrogenic blood loss will occur from too frequent phlebotomies. When anemia is expected, a donor should be identified, cross-matched, and be readily available when needed. The anemia of chronic disease might even benefit from Epogen treatment, but here again judicious use is important in order to avoid autoimmune destruction of the cat's red blood cells.

Hepatic Encephalopathy

This is a critical part of treating any cat with severe liver disease. The major strategies include avoiding the onset of hypokalemia or metabolic alkalosis; treating GI bleeding vigorously and expediently; maintaining normal blood pressure; avoid protein administration; and maintain normal fluid, pH and serum electrolyte balance.

Adjusting enteric bacterial flora is sometimes necessary and this can be brought about by several different methods. Neomycin or metronidazole can be given orally in order to remove the bacteria that are producing ammonia within the intestinal lumen. Retention enemas containing neomycin and saline in a proportion of 7:1 can also be used if the cat is comatose or where oral medication is otherwise restricted as occurs with severe vomiting. Lactulose solution can also be used to adjust the bacterial flora through its ability to maintain an acidic environment within the lumen of the colon thereby preventing the conversion of ammonium to the more absorbable ammonia.

General Patient Care

Any care delivered to cats should always include measures that consider their species requirements for gentle handling, minimal restraint, and measures taken to keep them as clean as possible. Baths should be given to remove any soiling from feces or urine. All catheters should be inspected for potential sites of contamination or underlying skin inflammation and any such occurrences should be managed as soon and as appropriately as possible. Any medications that are not necessary should be omitted and care should be taken to avoid drug interactions. Intravenous catheter sites should be ideally rotated every 3 to 4 days, but because of the logistical difficulties encountered with the cat being such a small species, many intravenous catheters can be retained for as long as 7 days without consequence, but under such conditions extremely meticulous catheter care is essential.

BILE PERITONITIS — WHITE BILE

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Effusions due to the release of bile into the abdominal cavity resulting in bile peritonitis are often in the exudate category. The effusion is typically greenish to yellow-orange and this color to the effusion often causes one to consider bile peritonitis. The nucleated cells in the effusion are composed of variable numbers of neutrophils, macrophages, mesothelial cells, and lymphocytes. Cytologically, phagocytized bile pigment appears blue-green to yellow and often can be seen within macrophages and/or extracellularly. Diffuse bile peritonitis is readily suspected clinically by the color of the fluid and cytologic findings. Bilirubin levels should be measured in the serum and abdominal fluid and diagnosis is confirmed by documenting abdominal fluid bilirubin levels greater than twice the serum bilirubin levels.

Occasionally bile peritonitis occurs where minimal or no bile pigment is visible on cytologic evaluation of the abdominal fluid and the primary finding is a basophilic, amorphous, extracellular, mucinous material that appears fibrillar. The mucinous material is acellular but inflammatory cells from the effusion are often caught up in the material. Abdominal fluid bilirubin concentration is often many times greater than the serum bilirubin level. The clear biliary fluid is thought to originate from the common bile duct epithelium. Extrahepatic biliary obstruction is thought to lead to biliary stasis and the biliary epithelium produces a clear, bile free mucoid material. A tear in the extrahepatic biliary tree or a ruptured gallbladder releases this material into the abdominal cavity resulting in bile peritonitis with "white bile."

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THE COMPLETE URINALYSIS

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Complete urinalysis should be performed every time a need to evaluate the renal system exists. Routine urinalysis can easily and accurately be performed in a veterinary practice. There are different components of a complete urinalysis; the physical examination (gross inspection of the urine), the chemical examination ("dip stick" test), and the microscopic examination. These should be performed soon after the collection of the urine specimen.

URINALYSIS – PHYSICAL EXAMANATION

The gross inspection of a urine specimen can provide significant information regarding any identifiable disease process involving the urinary system. Some of the more common or useful physical features of urine specimens are outlined briefly below.

Color

Color of the urine can provide potential insight into the various formed elements of the urine. Red urine is seen with either hemoglobinuria or intact erythrocytes. With intact erythrocytes, the supernatant of the urine should be clear following centrifugation where erythrocytes are forced into a pellet in the centrifuge tube. Brown-red colored urine may be seen associated with myoglobinuria or oxidized hemoglobinuria. Dark yellow colored urine may be seen associated with marked bilirubinuria.

Turbidity

Turbidity of any type of a fluid specimen is related to particular matter in that specimen. With turbid urine specimens, the particles that more commonly give the urine a turbid appearance include bacteria, inflammatory cells, erythrocytes, and crystals.

Odor

A strong ammonia odor to a urine specimen may suggest breakdown of urea, which should be in relatively high concentrations in a normal urine specimen, into ammonia by urea splitting bacteria. This simple physical feature of a urine specimen may provide immediate information regarding underlying bacterial infection of the urinary tract.

Specific Gravity

Specific gravity is commonly estimated from the refractive index of a urine specimen with the use of a refractometer. The specific gravity is predicated upon the presence of a concentration of small solutes. It is used as a simple measure of the ability of the kidney to concentrate or dilute a urine specimen and in conjunction with the measurement of serum urea nitrogen or creatinine, proves essential in the classification/identification of "renal failure". Selected solutes in high concentration (eg, glucose and protein) that normally should not be present in typical urine specimens may contribute slightly to the specific gravity/refractive index of the urine.

URINALYSIS – CHEMICAL EXAMANATION

Almost anything that can be measured in the serum or plasma of an animal with routine laboratory clinical chemistry methodologies can be measured in urine specimens. The most commonly performed chemical test in veterinary medicine is the simple dry chemistry reagent strip (dipstick). If one follows the instructions carefully, the volume of urine collecting on each of the reagent pad is very precise and the results obtained are relatively accurate. It is critical for some of the tests to read the color change result precisely at the time suggested by the manufacturer for that particular test. If the reagent strips were maintained in a desiccant at room temperature as is suggested by the manufacturer and if the dipping process is followed correctly, as the manufacturer suggests, the results are extremely valid. The primary problem that most people will encounter is when they are working with a urine specimen that is darkly colored red or brown-red. This coloration of the urine often interferes with accurate characterization of the color change taking place on the reagent strip. In this case, one must rely on backup chemical testing procedures that are more labor intensive and more expensive than the reagent strip. These specialized chemical tests are not routinely performed in a veterinary practice but can be performed in most reference laboratory facilities. Some of the more common dry chemistry reagent strip tests are listed below with abbreviated comments on interpretation. Detailed information is typically provided with the individual strip information inserts to include comments regarding interfering substances and overall interpretation; review of this information is recommended.

pH

Multiple factors influence the pH of a urine specimen. Some of these include rate of renal excretion of hydrogen ions (H^+), renal resorption of bicarbonate (HCO_3^-), sample age, and the presence of urea splitting bacteria causing an increase in pH. Knowledge of the urine pH may give some insight into the overall metabolic acid–base status of an animal if electrolyte distributions in the plasma are not seriously abnormal. Knowledge of the urine pH may also be helpful in interpreting other components of the urine. For example, severely alkalotic urine samples with a pH > 8.0 may have significant disintegration of RBCs, WBCs and casts, which will make it difficult to identify these abnormal formed elements in a urine specimen. Crystal identification may be aided with the knowledge of the pH also.

Protein

Protein determination in a urine specimen can be accomplished by different methods. The dipstick pad for protein is extremely sensitive for albumin but relatively insensitive to globulins and for some globulins such as Bence-Jones proteins (light chains of immunoglobulins) the pads are almost completely insensitive. The test pad is dependent upon reaction of the amino groups of proteins to react with the color of the acid–base indicators in the pads. False positives are reported for significantly alkaline urine samples. Certain types of detergents (quaternary ammonium compounds) may cause false positive reactions also. Interpretation of the dipstick protein pad must be made in light of other information about the urine (eg, inflammation and hematuria). The dipstick protein pad is used as a preliminary screen for proteinuria related to renal causes (glomerular or tubular). If the urine is not concentrated, a 1+ protein result is considered significant; however, if the urine is concentrated, a 2+ protein result is required before any significance is suggested. Sulfosalicylic acid (SSA) precipitation test is commonly used in most reference laboratories to confirm proteinuria suggested by the dipstick result. However, both tests should be considered screening (semi-quantitative) tests. True chemical determinations can be performed for more accurate protein quantitation and determination of the urine protein: urine creatinine ratio can help in assessing the degree of proteinuria present.

Glucose

Because of the ability of the proximal renal tubules for resorption of any plasma glucose that might make it through the glomerular filtrate, glucose concentrations in urine of clinically normal animals are extremely low and below the level of sensitivity for detection by the dipstick dry pad for glucose. True persistent glucosuria is associated with persistent or prolonged hyperglycemia in most cases; some cases of tubular dysfunction (Fanconi syndrome) may result in glycosuria without persistent hyperglycemia. False-positive reactions with the dipstick pad for glucose may happen with exposure to formaldehyde, the use of outdated pads or the presence of hydrogen peroxide. False-negative reactions can occur with high concentrations of ascorbic acid (inhibits the reaction pad) or some selected drugs like salicylates or tetracyclines.

Ketones

The ketone dipstick pad primarily measures the presence of acetoacetic acid and acetone; beta-hydroxybutyrate is not detected. The presence of measurable ketones in the urine indicates abnormalities in metabolism of fat (starvation or malnutrition, unregulated diabetes mellitus, sheep pregnancy toxemia, bovine ketosis, etc.). More sensitive qualitative tests for ketones are available if there is a questionable result.

Bilirubin

Accurate measurement of the bilirubin pad on the dipstick is often difficult because the degree of color change is relatively subtle and the yellow discoloration of the urine sample with bilirubin interferes with accurate detection of these subtle changes. Interpretation is different with different species. The dog has a low renal threshold for bilirubin; therefore, bilirubin is present and identified as a trace to 1+ result in most canine urine samples. Significantly concentrated canine urine samples have 2+ bilirubinuria as well as the presence of bilirubin crystals in the urine even when there is no hyperbilirubinemia. The cat on the other hand has a high threshold for bilirubin and essentially any detection of bilirubin in the urine of cats is significant. Significant bilirubinuria is used to support cholestasis or hemolytic disease. False-negative bilirubin results are possible with old urine samples because of degradation (hydrolysis) of conjugated bilirubin or because of conversion of bilirubin to biliverdin when exposed to UV light. Also, high concentrations of vitamin C can inhibit the reaction pad giving a false-negative result. Backup qualitative tests for bilirubin are available if there is any question in the result from the dipstick.

URINALYSIS – MICROSCOPIC EXAMANATION

Microscopic examination of urine sediments requires the availability of a good quality microscope. If one is not available accurate assessment of the formed elements of the urine will not be possible. Both a good 10x and 40x objective is required on the microscope. When examining the urine sediment microscopically, most people use a bright field microscope that is used for routine hematology and cytology specimens. When examining the urine specimen, putting the light out of bright field microscopy settings by lowering the substage condenser and partially closing the iris on the microscope may prove helpful in making various formed elements easier to visualize. The preparation of the sediment requires only a simple tabletop centrifuge with a relatively slow speed to allow sedimentation of the formed elements without mechanical damage to these elements. Most people examine the sediment on unstained preparations, but there are a series of commonly used stains including some developed specifically for urine sediment examination (Sedi Stain) or routine Romanovsky stains commonly used in hematology or cytology specimen analysis (Diff Quik, Wright's stain, etc.). The initial examination of an unstained specimen will be difficult. However, learning how to read these specimens precludes the observation of stain precipitate and misidentifying this as an organism or crystal and prevents the bacterial or fungal contamination of the stains with subsequent overgrowth and misinterpretation of the presence of these organisms. Practice with some pseudo urine specimens by using a clean urine specimen spiked with various "formed elements" commonly seen in urine sediment specimens. Epithelial cells from the buccal mucosa (spatula gentle scraping of the oral cavity), leukocytes and erythrocytes from anticoagulated whole blood originally submitted for hematology evaluation, and potential neoplastic or various inflammatory cell populations from other specimens (fine needle aspirates of solid masses, sediment smears of effusions, etc.). Some of the more commonly encountered formed elements in urine are briefly discussed below.

CELLS

Erythrocytes

Red blood cells in the urine, hematuria, can originate from any region of the urinary tract but most commonly is associated with local bleeding in the urinary bladder associated with cystitis or it is iatrogenic during the collection process. In fresh urine, close examination reveals their biconcave shape. In dilute urine, erythrocytes swell and lyse resulting in hemoglobinuria rather than hematuria. In concentrated urine, erythrocytes typically crenate and resemble crenated erythrocytes in the peripheral blood with multiple short uniform sharp cytoplasmic projections. Practice in the identification of these cells in urine is relatively simple. Place a drop of EDTA anticoagulated blood into dilute, non-concentrated and concentrated urine samples and see the effect on the erythrocytes.

Leukocytes

White blood cells are commonly seen with cystitis or any other type of inflammatory disease in the urinary tract. Typically only very few leukocytes are seen in normal urine (less than 2 WBC/HPF). These cells are usually spherical and in contrast to the erythrocytes, nuclei are visualized with careful inspection at 40x objective magnification field of view. Neutrophils are the most common leukocyte seen in urine and the lobed nucleus is usually very easy to identify even in unstained preparations. Mononuclear leukocytes, monocytes, macrophages and lymphocytes, have rounded to slightly indented nuclei. If there is ever a question regarding the identification of leukocytes or recognizing what type of leukocyte is present, preparation of an air-dried smear of the urine sediment and staining with a stain you use for hematology is recommended. This will allow direct detailed visualization of nuclear and cytoplasmic morphology similar to evaluation of a blood film.

Epithelial Cells

Differentiation between renal tubular, transitional and squamous epithelial cells from different regions of the urinary tract may take some practice. These cells are generally larger than the leukocytes and they typically have more cytoplasm (lower nuclear/cytoplasmic ratios) than leukocytes. Squamous epithelial cells are commonly larger than transitional epithelial cells (two to four times larger than leukocytes) and renal tubular epithelial cells are generally only slightly larger than leukocytes. Transitional epithelial cells may take on a polygonal or irregular shape with variably prominent projections from the cytoplasm. Close inspection even in an unstained preparation should allow visualization of the relatively centrally located round to oval nucleus commonly seen in these epithelial cells. They may be present individually or in small cohesive clusters. Collection of relatively large numbers of transitional epithelial cells with catheterized specimens is common due to the mechanical sloughing during the placement of the catheter.

CRYSTALS

Most crystals found commonly in the urine of animals are not clinically significant. Fresh, unrefrigerated urine samples generally do not have crystals or have only very few. If a urine sample is allowed to stand for any period of time, crystals will form if the correct compounds are present, particularly in a supersaturated specimen. Most crystals have typical morphologic appearances that allow identification. Knowledge of the dependency of pH on the formation of crystals may prove helpful also. Certain crystals will form only under certain pH situations.

CASTS

Casts are formed in the tubules of the kidney as a result of clumping of cells or other material within a protein matrix. These formed elements of the urine sediment prove to be helpful indicators of renal disease. Except for protein casts, renal tubular casts indicate tubular damage. Accurate identification of the various casts may be difficult because there is actually a transition between the different types of casts. In addition, they may have different formed elements including cells, granular proteinaceous cellular debris, protein, and fat. Casts are identified by several common features. These cylindrical structures have parallel sides and typically one end of the cast is irregularly ragged and the other end is potentially smooth and blunted. The ragged end represents the end of the cast that has broken off any remaining cast material within the renal tubules. The smooth end represents the end of the renal tubular thrombus, which represents the cast that eventually is sloughed and potentially identified in the urine sediment.

MISCELLANEOUS COMPONENTS OF THE URINE SEDIMENT

A variety of components may be found in the urine of normal and abnormal animals. Bacteria identified as uniform small round (coccal) to short rod-shaped structures that elicit “Brownian motion” because of their small sample size. If there is ever a question related to the accurate identification of bacteria, air-dried sediment of the urine stained with the stain commonly used in hematology can be helpful in characterizing these small particles. Yeasts and other structures including contaminating fungal forms from the environment may be found in urine also. Sperm may be seen and are typically easy to recognize based upon the distinctive structure and the fact that many will be viable and motile in a fresh urine specimen. Structures such as filter / fiber fragments and mucus strands may prove interfering with the accurate identification of casts. Glove powder must not be confused with crystals that are truly formed in the urine.

CYTOLOGY OF INFLAMMATION

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INFLAMMATORY CYTOLOGY

If the reaction is strictly inflammatory, then the left side of the flow chart shown in Figure 1 in the companion article, General Approach to Cytologic Interpretation, in this proceedings is followed. The inflammation must first be classified as neutrophilic/eosinophilic, mixed, or macrophagic. Classification is done arbitrarily and is based solely upon the relative proportions of the various inflammatory cells in the reaction. If neutrophils (or eosinophils) predominate (greater than 80% of the inflammatory cells present), the reaction is classified as neutrophilic (suppurative or eosinophilic). If neutrophils and mononuclear cells are present in approximately equal numbers (50% to 80% polymorphonuclear, the remaining cells mononuclear) then the response is termed mixed. When mononuclear cells predominate (greater than 50% of the inflammatory cells present) the reaction is classified as macrophagic (nonsuppurative, histiocytic).

Many inflammatory reactions can be even further subdivided on the basis of morphology of the various cell lines. The purpose of subclassification is to provide information regarding pathogenesis of the reaction and to aid in the identification of etiology. A detailed summary of the different classes and subclasses of inflammatory reactions is found in Table 1.

NEUTROPHILIC INFLAMMATION

Neutrophilic inflammation has two subtypes: neutrophilic with nondegenerate neutrophils, and neutrophilic inflammation with degenerate neutrophils. Nondegenerate neutrophils are either morphologically similar to those of peripheral blood or exhibit nuclear hypersegmentation. Degenerate neutrophils have characteristic nuclear and cytoplasmic changes.

Nuclear changes in degenerate neutrophils include hyalinization and selling of nuclei (an early stage of karyolysis), pyknosis, karyorrhexis, and karyolysis. Pyknotic nuclei are intensely stained and homogeneous without internal chromatin patterns. Karyorrhectic nuclei are generally pyknotic and have been fragmented into small pieces. Karyolysis is the process of spontaneous dissolution of the nucleus and is recognized as the streaming of nuclear chromatin away from the nucleus into the cytoplasm. Karyolysis can only be recognized in intact cells.

Cytoplasmic features of degeneration in neutrophils are generally more subtle than nuclear features. The cytoplasm becomes homogeneous, glassy and somewhat basophilic.

Neutrophilic inflammation with nondegenerate neutrophils is the result of severe irritation. In most cases, etiologic agents are not observed and the aspirated material will be sterile upon cultural examination. Classification of a reaction as neutrophilic with nondegenerate neutrophils is based upon the morphology of the majority of neutrophils; occasional dead neutrophils with pyknotic and karyorrhectic nuclei are expected even in the purest response.

Neutrophilic inflammation with degenerate neutrophils indicates that there is not only severe irritation but also that there is destruction of neutrophils. Of all the degenerative changes, nuclear hyalinization and swelling and karyolysis are the most significant because they indicate acute cell death. Acute cell death in neutrophils results for the effects of local toxins. The most common toxins are bacterial, and whenever karyolysis is present sepsis should be suspected even if bacteria are not seen. Culture of these samples is always recommended.

MIXED AND MACROPHAGIC INFLAMMATION

Like neutrophilic inflammation, mixed or macrophagic inflammatory reactions may also be subclassified based upon the morphology of their neutrophils. Interpretation of neutrophil degeneration in these instances is the same as for neutrophilic reactions. In general, however, mixed or macrophagic reactions imply less severe irritation than neutrophilic reactions and the neutrophils are usually either nondegenerate or only mildly degenerate. Of greater importance than neutrophil morphology in mixed and macrophagic inflammation is macrophage morphology.

Typical microphages are large, round to oval cells (20–35 μm) with eccentric round to oval or irregular nuclei. Nuclei have a lacy or reticulate chromatin pattern. Cytoplasm is abundant, granular, and faintly eosinophilic. Cytoplasmic vacuoles are present and generally contain phagocytized material. Phagocytized material is in most cases indistinct cellular debris or RBCs; however, in some instances, specific etiologic agents may be observed.

If all macrophages are of this typical morphology then mixed or macrophagic inflammatory reactions cannot be further classified. However, many mixed inflammatory responses also contain epithelioid cells, inflammatory giant cells, or both. Epithelioid cells are morphologically similar to typical macrophages except that their cytoplasm contains either no or only small vacuoles, and phagocytized material is absent. Inflammatory giant cells are large, multinucleated macrophages, which may contain phagocytized material or have cytoplasm resembling that of epithelioid cells. Nuclei are discrete, typical macrophage nuclei and may be located peripherally at the cell margin or aggregated centrally.

Whenever epithelioid and/or inflammatory cells are present, a mixed or macrophagic reaction can be further classified as pyogranulomatous or granulomatous, depending upon the prevalence of neutrophils. Whereas classification of a response as mixed or macrophagic suggests nothing specific regarding etiology and may be

Table 1. Subclassification of Inflammatory Reactions

Type of Inflammation	Primary Cytologic Feature	Morphologic Subtypes	Interpretation and Etiologic Significance
Neutrophilic	>80% neutrophils	1. With nondegenerate neutrophils	Severe irritation
		2. With degenerate neutrophils	Severe irritation; often septic
Mixed	50–80% neutrophils remaining cells mononuclear	1. With epithelioid cells and/or inflammatory giant cells (pyogranulomatous)	Low-grade irritant; consider foreign body, systemic mycoses, actinomycotic infection
		2. Without epithelioid cells and/or inflammatory giant cells (nonspecific)	Resolving neutrophilic/ eosinophilic reaction; low-grade irritant
Macrophagic	>50% macrophages	1. With epithelioid and/or inflammatory giant cells (granulomatous)	Low-grade irritant; consider foreign body, systemic mycoses, actinomycotic infection
		2. Without epithelioid and/or inflammatory giant cells (nonspecific)	Resolving neutrophilic/ eosinophilic reaction; low-grade irritant
Eosinophilic	Moderate to high numbers of eosinophils, other cells vary with subtype	1. With neutrophils	Allergic reaction
		2. Mixed	
		3. Granulomatous	

associated with resolving neutrophilic inflammation as well as with more traditional causes of low-grade irritation, classification as pyogranulomatous or granulomatous suggests that a foreign body, mycotic, actinobacterial or mycobacterial etiology should be considered. Often, these etiologic agents can be demonstrated cytologically.

EOSINOPHILIC INFLAMMATION

Inflammatory reactions characterized by noticeable numbers of eosinophils are generally the result of allergic phenomena and merit separate consideration. Causes include parasitic disease, mast cell tumors, asthma and systemic atopic responses. Eosinophils are rarely the principal cell seen; rather, they represent a prominent accompaniment of a neutrophilic, macrophagic or mixed inflammatory reaction. Eosinophils in these responses may be quite transient; we have seen a number of parasitic diseases where treatment resulted in a disappearance of eosinophils from the reaction in as few as 48 to 72 hours. Indeed, in these instances, abatement of the eosinophil numbers is a useful index of response to therapy.

IMPORTANT CONSIDERATIONS IN THE CYTOLOGIC EVALUATION OF INFLAMMATION

Several points regarding cytologic classification of inflammation are worthy of emphasis at this juncture. First, numbers of the various inflammatory components are always estimated, never counted. Uneven distribution of cells in cytologic specimens makes counting differentials unreliable. Second, inflammatory cytology should not be regarded primarily as an indicator of lesion duration but rather is best regarded as an indicator of the level of tissue irritation. Type of inflammation often provides significant help in identifying underlying etiology. Finally, inflammatory cytology also has utility in following the course of an inflammatory reaction or the response to therapy.

Consider the horse with an acute volvulus. Cytologic evaluation of the peritoneal fluid is commonly used to gauge the stage and severity of the reaction in such patients. The primary problem for the animal with volvulus is ischemia of the gut with eventual ischemic necrosis. Early in the disease, reduced blood flow leads to severe irritation of the involved bowel segment. At this stage cytologic evaluation of peritoneal fluid reveals neutrophilic inflammation with nondegenerate neutrophils and the prognosis for surgical intervention is good. If correction does not occur at this stage, the condition will likely worsen. Stasis of intestinal contents leads to bacterial proliferation and turnover with the release of bacterial toxins. These toxins can seep through the intestinal wall in to the peritoneal cavity. At this stage peritoneal fluid cytology reveals neutrophilic inflammation with degenerating neutrophils and prognosis for surgical corrections is only fair.

With continued hypoxia, integrity of the bowel wall becomes increasingly compromised until ischemic necrosis begins. At this stage, bacteria from the bowel gain access to the peritoneal cavity. Initially, the majority of these organisms are quickly phagocytized by neutrophils containing bacteria, or septic peritonitis. Prognosis is guarded. Advancing necrosis results in freer access of organisms to the cavity until the capacity of the inflammatory response to contain the bacteria is overwhelmed. This is reflected cytologically by the presence of a variety of types of bacteria both free in the background of the slide as well as within the cytoplasm of severely degenerate neutrophils. Such a finding cytologically dictates a poor to unfavorable prognosis; these animals generally do not recover.

CYTOLOGY OF BLOOD

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Blood films are generally examined following methanol fixation and staining with Romanowsky-type stains such as Wright or Wright-Giemsa. Rapid stains such as Diff-Quik are satisfactory, but are generally not of as high quality as Wright or Wright-Giemsa stains. These blood stains allow for examination of erythrocyte, leukocyte and platelet morphology. The new methylene blue wet mount stain or a reticulocyte stain is needed to stain for reticulocytes and Heinz bodies. For veterinarians who perform CBCs in their practices, it is essential that they and/or their technician are competent in the examination of stained blood films. Even when veterinarians send their CBCs to a commercial laboratory, the examination of stained blood smears can provide fast, useful information in emergency and after-hours situations.

It is important that an organized approach be made when examining a blood smear so that maximal information can be obtained. The smear is scanned initially at low magnification to estimate the total leukocyte count and to examine for the presence of large platelet aggregates, low numbers of abnormal cells, and microfilaria that might be missed during the differential count. One should always examine the feathered end of glass slide smear preparations since platelet aggregates, large cells, microfilaria, and sometimes leukocytes, tend to be pushed out and concentrated at the end of the slide. We estimate the total blood leukocyte count (cells/µL) by determining the average number of leukocytes per field using 10x or 20x objectives and multiplying by 150 or 500, respectively. For example, if 100 cells were counted per field using the 10x objective, the estimated total leukocyte count would be 100 x 150 = 15 $\times 10^3$/µL. These factors may need to be modified depending on the microscope used. With experience, one can look at stained blood films and get a rough estimate of cell numbers without actually counting the cells. These estimates provide useful information when an automated cell count is not available and provide a source of quality control when an automated cell count is also done.

After the leukocyte count is estimated, a differential leukocyte count is done using a 40x or 50x objective. It is the absolute number of each leukocyte type that is present, not the percentage that is important. Relative values (percentages) can be misleading if the total leukocyte count is abnormal. As an example let us consider two dogs, one with 7% lymphocytes and a total leukocyte count of 40,000/µL and one with 70% lymphocytes and a total leukocyte count of 4,000/µL. The first might be classified as a relative lymphopenia and the second as a relative lymphocytosis, but both cases, in fact, have the same normal absolute lymphocyte count (2,800/µL).

The presence of a high neutrophil count does not necessarily indicate inflammation, since neutrophilia may occur from epinephrine release and endogenous or exogenous glucocorticoids. The presence of a lymphopenia, an eosinopenia and, in the dog, a monocytosis along with a neutrophilia is indicative of stress or exogenously administered glucocorticoids. Significant left shifts do not occur with glucocorticoid or epinephrine-induced (physiologic) neutrophilia; consequently, the presence of a left shift is usually indicative of purulent inflammation. However, some noninfectious conditions (eg, autoimmune hemolytic anemia in dogs) may also have an associated left shift. The presence of toxic cytoplasm (foamy basophilia and/or Döhle bodies) along with a left shift is suggestive of a primary or secondary bacterial infection. It is beyond the scope of this presentation to consider all abnormal leukogram patterns. Suffice it to say that much information can be gained from a differential leukocyte count.

Following the differential leukocyte count, one should examine erythrocyte morphology and evaluate the number and morphology of platelets present using the 100x objective. While rouleaux formation of erythrocytes is normal in cats, prominent rouleaux formation in dogs is most often an indicator of the presence of an inflammatory process.

If an animal is anemic, it is especially important to evaluate blood smears for the presence of polychromasia. Most canine reticulocytes and the aggregate reticulocytes of cats will appear blue to bluish-red when properly stained with routine blood stains. Increased polychromasia provides evidence of a regenerative response to anemia and indicates that the anemia is the result of either blood loss or increased erythrocyte destruction. A lack of polychromasia indicates a lack of bone marrow response in the dog, which may be the cause of the anemia. In mild anemia in cats, punctate reticulocytes may be released from the bone marrow without an accompanying release of aggregate reticulocytes. Since punctate reticulocytes contain insufficient RNA to make these cells appear polychromatophilic with routine blood stains, a lack of polychromasia does not necessarily indicate a nonregenerative anemia in mildly anemic cats. If staining is not optimal, it may be difficult to determine the degree of polychromasia. In this case, a reticulocyte stain should be prepared to determine if a reticulocytosis is present.

The presence of various erythrocyte shape abnormalities may provide information concerning the cause of an anemia or nature of the disease process present. For example, the presence of frequent spherocytes in dogs indicates the likelihood of an immune-mediated hemolytic process. The presence of schistocytes, along with decreased platelets, in dogs suggests that disseminated intravascular coagulation may be present. The presence of acanthocytosis, polychromasia and frequent nucleated erythrocytes in dogs should result in hemangiosarcoma being placed high on the list of differential diagnoses. The presence of unstained "spots" and/or nipple-like projections in erythrocytes may indicate the presence of Heinz bodies. When Heinz bodies are suspected, it is wise to verify their size and number using a reticulocyte stain. Cats may have up to 5% small to medium Heinz bodies normally, and increased numbers may occur in association with certain metabolic disorders and in cats eating soft-moist cat foods containing propylene glycol. Consequently, the finding of Heinz bodies in cats does not necessarily indicate drug-induced oxidant injury. In addition to Heinz bodies, oxidant-induced injury to canine erythrocytes may result in the formation of eccentrocytes (erythrocytes where the hemoglobin is concentrated to one side of the cell).

The presence of hypochromic-appearing erythrocytes is strongly suggestive of iron deficiency. This conclusion is supported by finding a low mean cell volume (MCV) and confirmed by finding a low serum iron concentration and normal or increased total iron binding capacity. With the exception of nursing animals, nearly all cases of iron deficiency result from chronic blood loss. Although not specifically diagnostic for lead poisoning, the presence of basophilic stippling, especially when accompanied by circulating nucleated erythrocytes, is highly suggestive of this toxicity.

Various infectious agents including hemotrophic mycoplasmas, *Babesia*, *Ehrlichia*, and *Anaplasma* organisms may be seen in stained blood films. It is important to differentiate organisms from stain artifacts, Howell-Jolly bodies and platelets overlying erythrocytes. Generally bacteria occur in too low of numbers in bacteremia to be found on blood smears. When found, it is important to determine that they are not stain contaminants.

Blood smears from dogs and cats normally average between 12 and 35 platelets per field when examined using the 100x objective. We generally estimate their numbers by multiplying the average number per 100x field by 15,000 to get the number of platelets x10^3/µL of blood. For example, if about 15 platelets are present in each 100x field, the estimated platelet count would be 15 x 15,000 = 225 x10^3/µL. While special attention will be given to the estimation of platelet numbers in animals with hemostatic diatheses, it is important to routinely estimate the platelet numbers on blood films, because many animals with thrombocytopenia exhibit no evidence, or past history, of bleeding tendencies. If a thrombocytopenia is suspected, it should be confirmed with a platelet count. The presence of frequent large platelets in association with a thrombocytopenia suggests that the thrombocytopenia probably results from destruction or utilization rather than decreased production. A major exception to this statement is that platelets may be large in association with myeloproliferative disorder where their production is defective.

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CYTOLOGY OF INTERNAL ORGANS

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Exfoliative cytology can be obtained using imprints of tissues excised during surgical procedures. This provides rapid information (and occasionally details not recognized in histologic sections), but generally more definitive information is obtained by fixing excised tissue in formalin and submitting it for embedding, sectioning, staining with H&E, and evaluation by a veterinary pathologist. The major advantages of histologic sections are that tissue architecture is preserved and more cells are usually available for examination. In addition to more rapid information, fine needle aspirate cytology involves less cost to the client and less trauma to the animal. In the past, high quality exfoliative cytology samples could be obtained from internal organs by fine needle aspiration if the tissue/lesion was large and palpable and the pathologic changes were uniformly distributed. If the tissue or organ to aspirate was small (eg, enlarged adrenal gland) or lesions were focal within a tissue or organ (eg, focal tumor metastasis to the lungs), fine needle aspiration often failed to yield diagnostic material. The availability of ultrasound machines and training in the use of these machines has greatly facilitated the collection of diagnostic, ultrasound guided aspirates of internal organs.

CELLULARITY AND TISSUE OF ORIGIN

Aspirate smears are generally prepared using a squash technique and stained with a Wright-type stain. It is important to note the cellularity (non-blood cells) of the samples obtained and the degree of blood contamination. Few non-blood cells are normally present in tissue aspirates from some organs such as lung and kidney, but many cells are normally present in aspirates from other organs such as liver and lymph nodes. Aspirates from liver and spleen naturally have large amounts of blood contamination not found to the same degree in high quality aspirates from other organs. If increased numbers of leukocytes are present, it is important to make sure they exceed the number present in blood before inflammation is diagnosed. For this reason, it is helpful to have a recent complete blood count (CBC) for comparison.

In addition to overall cellularity, one should identify the types of cells present and determine whether their morphology is consistent with the organ one is trying to biopsy. For example, if a lymph node is enlarged, are sufficient lymphocytes present to allow confirmation that the lymph node was successfully biopsied? Fine needle aspirates may be obtained from a variety of internal organs. This article discusses cytologic examination of aspirate smears for lung, liver, and lymph nodes.

CYTOLOGY OF LUNG ASPIRATES

Aspirates of healthy lung tissue have scant cellularity and variable amounts of blood contamination. Low numbers of respiratory epithelial cells are generally seen. Epithelial cells are cuboidal to columnar with light blue cytoplasm. Nuclei are generally oval with granular chromatin and located in the basilar end of the cell. Cilia may be present on the apical end of some columnar cells. Mucus-secreting goblet cells containing pink to purple cytoplasmic granules may be seen and sparse reddish ribbons of mucus may be present. Low numbers of pulmonary macrophages are a normal finding. When activated, they become large and heavily vacuolated and exhibit phagocytosis of cells and/or debris. Sheets of mesothelial cells are sometimes seen as a result of the needle penetrating serosal surfaces. They are cohesive, angular in shape, and uniform in size. Hepatocytes may also be present if the needle is inserted caudally in the chest and the diaphragm is penetrated.

A cellular lung aspirate is abnormal. Inflammation is indicated when increased numbers of inflammatory cells are present. Neutrophils and macrophages are most often seen, but variable numbers of eosinophils, lymphocytes, plasma cells, mast cells, and basophils may be present. When neutrophils predominate, the sample should be examined closely for infectious agents (especially bacteria), particularly if the neutrophils are degenerate. However, neutrophilic inflammation can also be present in other infectious disorders and noninfectious disorders including neoplasia, necrosis, and foreign body pneumonia.

Activated macrophages can have an epithelioid appearance and form aggregates. These epithelioid macrophages and multinucleate giant cells are characteristically found in granulomatous inflammation. When neutrophils are also prominent, the inflammation is referred to as pyogranulomatous inflammation. Causes of granulomatous or pyogranulomatous inflammation include fungal infections (including aspergillosis, blastomycosis, histoplasmosis, and coccidioidmycosis) and foreign body reactions.

When eosinophils compose more than 10% of the nucleated cells in lung aspirates, parasitic (including heartworms and lungworms) and hypersensitivity processes should be considered. When eosinophils are increased, on should examine a blood films to verify that the increase in not simply from blood contamination. Idiopathic eosinophilic granulomatosis (characterized by increased numbers of eosinophils and variable numbers of macrophages, neutrophils, plasma cells and basophils) occurs in dogs. Mixed inflammatory reactions occur in animals with protozoal (*Toxoplasma gondii* and *Neospora caninum*) pneumonia.

Hemorrhage may be indicated by the presence of erythrophagocytosis, hemosiderin within macrophages, and hematoidin crystals. The presence of abundant basophilic granular to amorphous material in the background, along with "ghost cells" where nuclear and cytoplasmic detail is lost, indicates that necrosis is present. Necrosis is common in the center of neoplastic and inflammatory disorders; consequently, one should try to obtain material from the periphery of lesions to determine the cause of the necrosis.

Neoplasia in lungs may be primary or metastatic, with the latter being more common. Cohesive clusters of basophilic anaplastic epithelial cells occur in carcinomas of lungs, as well as metastatic carcinomas other organs such as prostate, mammary gland, and bladder. With the exception of squamous cell carcinoma, it is generally not possible to determine the site of origin by the morphology of cells alone. Increased eosinophils may occur in dogs with bronchoalveolar carcinoma.

Cells from sarcomas are less cohesive than cells from carcinoma; therefore, they are often seen as individual elongated or spindle-shaped cells. Primary sarcomas in lungs, including osteosarcoma, fibrosarcoma, rhabdomyosarcoma, and schwannoma, are rare in dogs and cats; however, sarcomas from other organs can metastasize to the lungs.

Hemolymphatic neoplasms may be present in lungs, with lymphoma being most common. Malignant histiocytosis occurs in the lungs of dogs (especially Bernese Mountain dogs, golden retrievers, and flat-coated retrievers), but the lung is not a common site in cats. Lymphomatoid granulomatosis is a T-cell tumor in dogs that consists of large pleomorphic mononuclear cells together with infiltrates of lymphocytes, plasma cells, and eosinophils. Neoplastic cells may be in a minority, making it difficult to differentiate this disorder from inflammation (eg, eosinophilic granulomatosis).

CYTOLOGY OF LIVER ASPIRATES

Hepatocytes are the predominant cell type present in normal liver aspirates. These large epithelial cells have low nuclear to cytoplasmic ratios. Their nucleus contains a nucleolus that is sometimes prominent, and their cytoplasm often contains greenish black pigment that is predominantly lipofuscin. Intranuclear crystal-like rectangular structures may be present, especially in aged dogs. Normal hepatocytes are occasionally binucleated. Occasional clumps of small biliary epithelial cells with high N:C ratios and low numbers of mast cells may be observed. Sheets of angular, uniform mesothelial cells are sometimes seen as a result of the needle penetrating serosal surfaces. They must be differentiated from clumps of biliary epithelial cells and carcinomas.

Hepatocyte morphology can change with alterations in metabolism or in response to injury. The presence of discrete vacuoles in the cytoplasm of hepatocytes indicates the presence of lipid, which can fill the cytoplasm in hepatic lipidosis (a common disorder in cats). The presence of cytoplasmic rarefaction (cytoplasmic clearing or nondiscrete “foamy” vacuolation) indicates the accumulation of glycogen or water (hydropic degeneration). Endogenous hyperadrenocorticism and the exogenous administration of glucocorticoids result in the accumulation of glycogen within the liver. When glycogen accumulation is marked, it can result in hepatomegaly. This corticosteroid-induced hepatopathy is common in dogs. Hepatocellular injury, such as toxic insults and hypoxia, can result in hydropic (ballooning) degeneration, in which water accumulates following alterations to cell membranes and cytoplasmic organelles.

The presence of black ribbons of inspissated bile between hepatocytes indicates the presence of cholestasis, and increased numbers of macrophages containing black pigment generally indicate the presence of hemosiderosis.

Because of the substantial blood contamination associated with liver aspirate smears, it can be difficult to determine if inflammation is present. It is helpful to review a CBC collected on the same day to determine whether an increase in a specific cell type represents an inflammatory infiltrate or reflects an increased cell count in blood. The finding of inflammatory cells within clumps of hepatocytes provides evidence for inflammation. Neutrophilic inflammation may be seen in septic inflammation, nonseptic inflammation (eg, acute pancreatitis), and feline neutrophilic cholangiohepatitis. The cause of feline neutrophilic cholangiohepatitis is unknown but may be associated with extrahepatic diseases, including inflammatory bowel disease and acute pancreatitis. Increased numbers of small lymphocytes (and few plasma cells) is a common finding in older cats with lymphocytic portal hepatitis. The frequency with which this inflammatory process causes illness is unknown. A mixed inflammatory response including neutrophils and variable numbers of macrophages and lymphocytes is seen in cats with feline infectious peritonitis. Mixed cell inflammatory reactions may also occur in dogs and cats with fungal, protozoal, and mycobacterial infections. Eosinophils may be a prominent infiltrate in animals with eosinophilic enteritis, and in cats with hypereosinophilic syndrome and liver flukes.

Nodular regenerative hyperplasia of unknown etiology is common in aged dogs. Hydropic degeneration may be present in hepatocytes and variably increased numbers of inflammatory cells, including neutrophils, lymphocytes, and macrophages containing pigment and/or lipid, may be observed. Extramedullary hematopoiesis, especially involving granulopoiesis, may occur as a nonspecific reaction to nodular reactive hyperplasia and other chronic hepatic disorders in dogs.

The observation of ribbons of eosinophilic material associated with hepatocytes suggests the presence of amyloid deposits. Systemic amyloidosis occurs secondary to chronic extrahepatic inflammation. It appears to be a familial disease in Chinese shar pei dogs and Abyssinian and Siamese cats.

Primary hepatic neoplasia includes hepatocellular adenoma or hepatoma (with relatively normal-appearing hepatocytes), hepatocellular carcinoma (with mildly to markedly abnormal hepatocytes), and bile duct adenomas and carcinomas (both of which usually have relatively normal appearing bile duct epithelial cells). Hepatocellular neoplasms are more common in dogs and bile duct neoplasms are more common in cats. The liver is a frequent site of metastasis for hematopoietic neoplasms including lymphoma, lymphoid leukemias, myeloid leukemias, mast cell tumors, and malignant histiocytosis. In addition, carcinomas and sarcomas from the intestinal tract and pancreas often metastasize to the liver because of vascular drainage from these organs.

CYTOLOGY OF LYMPH NODE ASPIRATES

Lymphocytes are fragile and easily lysed during smear preparation; consequently, aspirate smears exhibit variable numbers of free nuclei and cytoplasmic vesicles (lymphoglandular bodies). Small lymphocytes (1–1.5 times the diameter of a RBC), account for 90% or more of the total nucleated cells in normal lymph nodes. Medium (2–2.5 times the diameter of a RBC) and large (>3 times the diameter of a RBC) lymphocytes account for 5% to 10% of the total nucleated cells in normal lymph nodes. Small lymphocytes have densely clumped nuclear chromatin and scant cytoplasm, and medium and large lymphocytes have less densely clumped nuclear chromatin, and variable amounts of cytoplasm. Nucleoli may be visible in some of these immature cells. Plasma cells, macrophages, and neutrophils may be present in low numbers, and rare mast cells may be seen. Perinodal fat may be present on the smear. Salivary epithelial cells may be present if the salivary gland is aspirate by mistake instead of a submandibular lymph node.

Reactive lymphoid hyperplasia occurs in response to local or generalized antigenic stimulation associated with septic or nonseptic inflammation and neoplasia in areas drained by the lymph nodes. Small lymphocytes predominate, but medium/large lymphocytes increase up to 15% of all nucleated cells, and plasma cells increase slightly to markedly in numbers. Slight increases in neutrophils, macrophages, or eosinophils may also be present. Idiopathic peripheral lymphadenopathy in young cats is an exception to the pattern described above. Medium/large lymphocytes predominate, mimicking a lymphoma. Spontaneous regression of the lymphadenopathy occurs over a period of weeks to months. A majority of cats are reported to be FeLV positive.

The term *neutrophilic lymphadenitis* is used when neutrophils exceed 5% of all nucleated cells in a smear with minimal blood contamination. Neutrophils may be increased in response to septic, nonseptic, and neoplastic disorders. The term *eosinophilic lymphadenitis* is used when eosinophils exceed 3% of all nucleated cells. Eosinophils may be increased in response to eosinophilic inflammation (eg, flea-bite hypersensitivity and feline rodent ulcers), hypereosinophilic syndrome, and as part of a paraneoplastic reaction to mast cell tumors (especially dogs) and less often certain lymphomas and carcinomas. Increased macrophages and multinucleated giant cells in granulomatous or pyogranulomatous inflammation occur in response to certain fungal, protozoal, protothecal, mycobacterial, and rickettsial disorders.

A wide variety of tumors metastasize to regional lymph nodes. Clusters of carcinoma cells are more easily recognized than individual round cells or sarcoma cells. Neoplastic lymphocyte infiltrates can be confused with reactive lymphoid hyperplasia if the neoplastic cells account for a minority of the total lymphocytes present.

Most lymphomas in dogs and cats are high-grade lymphomas consisting of medium to large neoplastic lymphocytes, that generally comprise 60% to 90% of all the nucleated cells. Lymphomas with lower numbers of neoplastic cells and low-grade lymphomas involving small lymphocytes may be difficult to recognize in aspirate smears. Lymphomas are classified in various ways using architecture on histopathology, lymphocyte morphology, and immunophenotyping (B cell versus T cell). It is not possible to definitively separate B-cell lymphomas from T-cell lymphomas by morphology alone, although some B-cell lymphomas have a plasmacytoid appearance and T-cell lymphomas may have more pleomorphic or convoluted nuclei.

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CHEMISTRY: PROFILING AND TRENDING

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Biochemical profiling is defined as the use of multiple blood chemistry determinations to simultaneously assess the health status of various organ systems. In addition to standard chemistry tests, other parameters (ie, hemograms, urinalysis) are measured to give a more accurate and complete picture of the overall health status of the patient. Strictly speaking, hemograms and urinalysis are not part of clinical biochemical profiles; however, biochemical profiles cannot be accurately interpreted without simultaneous evaluation of the complete blood count (CBC) and urinalysis.

Biochemical profiling is a powerful diagnostic and monitoring device used in ill patients and those receiving therapy. It is also an important component of regular wellness evaluations in healthy dogs and cats. Although biochemical profiling offers exciting potential as a clinical tool, it is not a panacea. The following paragraphs illustrate some of the more important difficulties encountered in the interpretation of clinical chemistry data.

Since standard chemistry screens may include from 12 to 30 different test results, interpretation of these data may be extremely complex. Furthermore, interpretation of results is often clouded by the fact that perfectly normal animals may have—indeed are expected to have—an occasional abnormal test result. It is estimated that in a standard panel of 12 chemistry tests, approximately 46% of all normal subjects will have at least one abnormal test result. Such abnormalities are usually associated with the way in which referenced (or normal) values are determined.

In order to establish the “normal range” reference values for a given test, the procedure is performed on samples from a large population of clinically normal individuals. The central 95% of the given results is identified and, if the data have a Gaussian distribution, a mean and a standard deviation are determined based on the central 95%. The reference values are then defined as those values falling within the central 95%, ie, within two standard deviations above and below the mean. Therefore, 5% of the values from a normal (ie, healthy) population fall outside the defined “normal” reference interval for any given parameter.

Just as healthy individuals may have occasional abnormal test results, patients with severe organ disease can have test results that lie within the normal reference intervals. For example, elevated alanine aminotransferase (ALT)—an enzyme normally found in the cytosol of hepatocytes—has long been considered an important indicator of liver disease in dogs. However, serum ALT levels will only be elevated under specific circumstances, eg, in conditions where there is injury to hepatocyte plasma membranes causing release of cytoplasm from membrane-bound vesicles. In more chronic liver disease, plasma membrane characteristics may be near normal. In addition, ALT levels reflect the number of hepatocytes with injured membranes; therefore, marked elevations are more commonly seen in diffuse rather than localized liver disease. ALT levels also will vary with the stage of organ disease at the time of sample collection. This enzyme has a circulating half-life of 2 to 4 days; therefore, a 2-fold elevation in ALT due to acute liver necrosis may be expected to return to near normal within a week.

The clinician must also be aware that physical compromise of one organ system may cause abnormal chemistry value sin tests that are used primarily to indicate disease in a different organ system. For example, calcium levels are used primarily as indicators of parathormone activity. However, serum calcium is partially bound to albumin filtrate. Consequently, anything that reduces albumin concentration may result in reduced calcium concentration, which could lead to erroneous conclusions about parathormone activity.

Key points in the practice of biochemical profiling:

- A single chemistry test should never be used to assess the total health status of an organ.
- Understand the factors affecting a given test results, such as the causes of elevations, circulating half-lives of components being measured, and routes of excretion.
- Consider the interactions between different organ systems and how the interaction can affect various test results.
- Only through the systematic assessment of data can misinterpretation and confusion be avoided.

Another key to understanding chemistry organ panels is to interpret them as a part of a larger laboratory profile that includes hemogram evaluation (the CBC) and urinalysis. The CBC and urinalysis provide general information regarding the patient. These should be interpreted first. The remainder of the chemistry panels assesses various organ systems and are best interpreted last.

The CBC includes white cell data, red cell data, platelet data, and total plasma protein. Leukogram data provide information regarding the presence of inflammation, stress, tissue necrosis, antigenic stimulation, systemic hypersensitivity or systemic toxemia. Erythrogram data provide information regarding the presence of anemia or polycythemia and also allows the classification of these syndromes into pathophysiologic subtypes. Platelet data indicate presence or absence of thrombocytopenia, which can be caused by destruction (immune-mediated), consumption (disseminated intravascular coagulation), or lack of production, or sequestration (hypersplenism). Increased total plasma protein suggests either hemoconcentration from dehydration or possible antigenic stimulation. Decreased plasma protein suggests loss through the gastrointestinal system, kidney, or blood loss or possible reduced protein production by the liver.

Complete urinalysis includes physical examination, chemical examination, and sediment examination. The complete urinalysis provides data regarding renal tubular concentrating ability, renal tubular integrity, urinary tract hemorrhage/infection, ketoacidosis, and cholestasis.

A final aspect of biochemical profiling is consideration of the value of trending. *Trending* refers to the evaluation of multiple chemistry panels over time in the same patient. Trending is of value both in health and disease. In healthy animals, trending provides a more personalized reference range, which can be used to recognize subtle changes as they occur with aging. In diseased animals, trending is used to gauge the progress of response to therapy.

GENERAL APPROACH TO CYTOLOGIC INTERPRETATION

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Once the cytologic specimen has been properly collected and stained, it is ready for examination under the microscope. The principal roles of the cytologist are to recognize and classify inflammatory reactions to identify any etiologic agent that may have caused inflammation, and to recognize the presence of malignant cells. In this article, we discuss the general guidelines that are followed in making such determinations.

SCANNING THE SLIDE

Cytologic interpretation begins with proper slide evaluation. Different kinds of specimens demand different approaches. For example, fluid smears are made in the same manner as peripheral blood films and consequently have a thick area (near the point of specimen application), a monolayer (towards the center of the smear) and a feathered edge (area most distant from the point of application). When fluid smears are examined, all three areas of the smear are evaluated, first at low magnification and later under oil immersion. Each area is examined for different features. For example, the most important area for evaluation of cell morphology is the monolayer. Large particulate material, large cells, or cells containing phagocytized material are generally found either in the thick portion of the smear or at the feather edge. Consequently, in the case of inflammatory reactions, classification requires mental integration of the relative numbers of the different cell types seen in the monolayer and at the feather edge. (See the companion article, Cytology of Inflammation, in this proceedings.) Since neutrophils concentrate in the monolayer and macrophages in the feather edge, it is easy to appreciate that examination in only one area can lead to misinterpretation of cytologic response.

Slides made by squashing, scraping, or impression smear techniques also require scanning at low magnification. In these cases, low magnification assessment is done to determine what part of the preparation is best for evaluation of cell morphology under oil. All squashing, scraping, and smearing techniques produce slides that vary in sample quality from area to area. Some areas are too thick to allow evaluation of cytologic detail, while in other areas a majority of the cells are broken. A cardinal rule of cytology is that only intact cells can be interpreted, so finding a monolayer area where cells are intact and cytologic detail can be observed is critical.

Whereas in fluid smears one must be concerned about cell distribution between the monolayer and feathered edge, in scrapings and squash preparations from aspirates this is not an issue because cell distribution is generally random. In contrast, cells in high quality impression smears are not randomly distributed but rather reflect cell distribution in the tissue imprinted. For example, aspirates taken from a reactive hyperplastic lymph node will have a random mixture of small lymphocytes, large lymphoblasts, and plasma cells (from medullary cords). Consideration of cell distribution in impression smears can therefore provide some information regarding tissue structure.

GENERAL APPROACH TO CYTOLOGIC INTERPRETATION

As the slide is scanned, cytologic interpretation begins. Because of the wide variety of specimen sources—effusions, lymph nodes, skin masses, internal organs, etc.— the novice at first may be overwhelmed by the variety of cells encountered. However, the beauty of diagnostic cytologic is that regardless of sample source, the general approach to interpretation is the same. This approach is summarized in the flow chart in Figure 1. Interpretation always begins with the answer to one basic question: How many cell types are present on the slide? Fortunately, there are only three possibilities. Either all of the cells are inflammatory (neutrophils, eosinophils, lymphocytes, plasma cells, or monocyte/macrophages), or all are non-inflammatory (of tissue origin), or the cytologic response is complex (both inflammatory and non-inflammatory). Specific approaches to classifying inflammatory responses and recognizing malignant neoplasia are covered in subsequent manuscripts. (See the companion article Cytology of Inflammation and Cytology of Neoplasia in this proceedings).

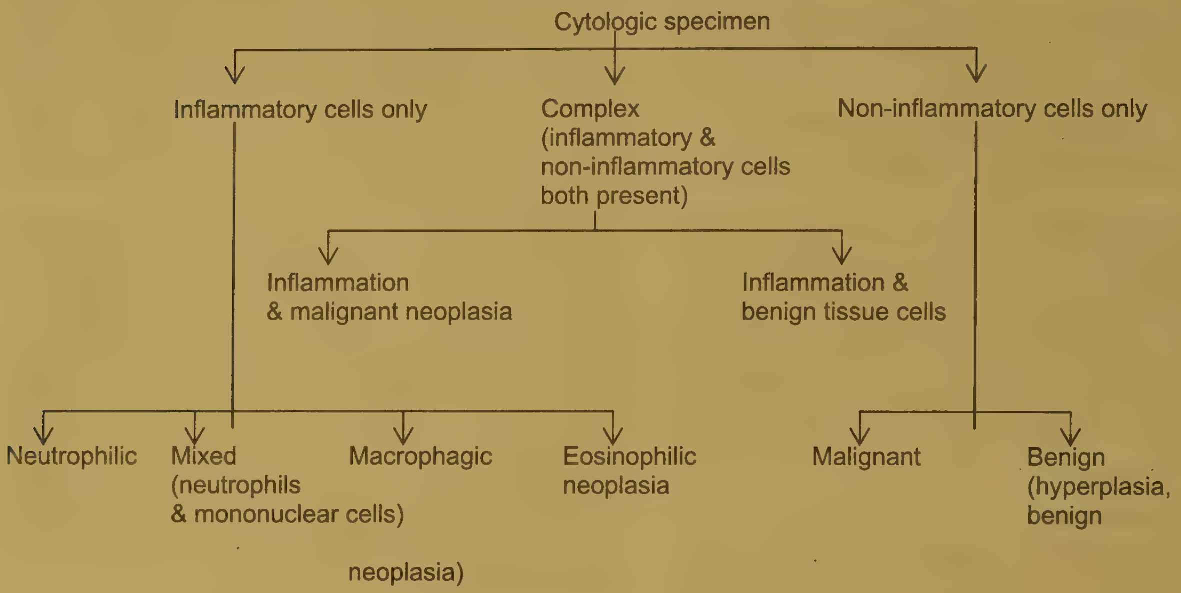
Cytologic specimen
Inflammatory cells only
Complex (inflammatory & non-inflammatory cells both present)
Non-inflammatory cells only
Inflammation & malignant neoplasia
Inflammation & benign tissue cells
Neutrophilic
Mixed (neutrophils & mononuclear cells)
Macrophagic
Eosinophilic
Malignant
neoplasia
Benign (hyperplasia, benign
neoplasia)

Figure 1. General approaches to cytologic interpretation.

CYTOLOGY OF NEOPLASIA

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CYTOLOGY OF MALIGNANT NEOPLASIA

Neoplastic processes may be either benign or malignant. It is virtually impossible to differentiate between benign neoplasia and hyperplasia cytologically, and these benign processes therefore are discussed together in a later section. Malignant neoplastic processes are identified through the recognition of specific malignant criteria exhibited by the cell population under consideration. Criteria of malignancy may be loosely classified into four categories:

1. General criteria of malignancy
2. Nuclear criteria of malignancy
3. Cytoplasmic criteria of malignancy
4. Structural criteria of malignancy

General criteria of malignancy refer to the appearance of the cell population as a whole. Malignant neoplastic processes are generally characterized as a uniform population of pleomorphic cells; that is, cells usually appear to be of a single cell type (for example, all mast cells or all spindle-shaped connective tissue cells) which exhibit variable cell size and variable nuclear size. These features can generally be recognized at low magnification and represent the first suggestion that the cytologic diagnosis is one of malignant neoplasia. While such pleomorphism in a uniform population of cells is easy to recognize in uncomplicated cases, the presence of large numbers of inflammatory cells may mask neoplasia. Therefore, whenever an inflammatory response is associated with a population of non-inflammatory cells, the non-inflammatory cells should be carefully scrutinized for evidence of malignancy. Inflammatory cells are commonly encountered in large numbers in cytologic preparations from oral or skin neoplasms with ulcerated surfaces.

Nuclear criteria of malignancy are the most important criteria employed in identifying a malignant neoplasm cytologically. Evaluation of nuclei for malignancy is best performed under oil immersion. Features suggesting malignancy (in Romanowsky stained preparations) include multiple nucleoli, large irregularly shaped nucleoli, coarse chromatin patterns (areas within the nucleus which stain intensely as well as other areas which are virtually unstained or only poorly stained), irregularities and indentations in the nuclear membrane and variable nuclear/cytoplasmic ratios among the cells seen. Mitotic figures per se are not a criterion of malignancy as they may be seen in hyperplastic cell populations (eg, lymph node hyperplasia); however, abnormal mitoses (eg, three or more planes of division) are a feature of malignancy. Multinucleated tumor cells are occasionally seen, but giant cells may also occur in inflammatory reactions (granulomatous inflammation). Since the nuclear criteria of malignancy are the most important in establishing the diagnosis of malignant neoplasia, the authors suggest that three to four such nuclear alterations be identified before the diagnosis of malignancy is suggested.

Cytoplasmic criteria of malignancy are considerably less important in establishing a diagnosis of malignant neoplasia but do provide supportive evidence. Cytoplasmic criteria include cytoplasmic basophilia, cytoplasmic vacuolation and variation in amounts of cytoplasm. Cytoplasmic features of malignancy suggest the primitive nature of the neoplastic population; for example, cytoplasmic basophilia results from a high cytoplasmic content of RNA, a constant feature of young proliferating cells.

After the nuclear and cytoplasmic criteria of malignancy have been used to establish the cytologic diagnosis of malignant neoplasia, the structural features of the neoplastic cells may be evaluated in an attempt to further classify the tumor as a carcinoma, sarcoma, or discrete cell neoplasm. Carcinomas are neoplasms of epithelial cell origin. Normal epithelial cells are generally adherent to one another and this property is generally reflected in cytologic preparations from epithelial cell neoplasms. Carcinoma cells are generally round to oval, and are arranged in sheets and clusters. Cells from neoplasms of glandular epithelium (adenocarcinomas) are often arranged in acinar patterns around a central lumen. Adenocarcinoma cells also often contain large vacuoles containing secretory product.

Sarcomas are neoplasms of cells of connective tissue origin. Connective tissue cells generally are embedded in a matrix, which they themselves secrete. Consequently, aspirates or imprints from sarcomatous masses are generally less cellular than cytologic preparations made from epithelial or discrete cell neoplasms. Structurally, connective tissue cells are usually spindle-shaped or flame-shaped (cells with tails) and this morphology is also typical of sarcomatous cells.

The sarcomas of veterinary significance include osteosarcoma, fibrosarcoma, liposarcoma, hemangiosarcoma, melanosarcoma, and chondrosarcoma. Osteosarcoma and chondrosarcoma cells are more commonly flame-shaped than spindle-shaped. In addition, aspirates from these two neoplasms may contain considerable matrix material—eosinophilic osteoid in the case of osteosarcoma and metachromatic (purple) chondroid in the case of chondrosarcoma. The cytoplasmic margin of osteosarcoma cells is often irregular and vacuolated. Melanosarcoma has several distinguishing cytologic features. Of principal importance is the presence of brown to black cytoplasmic granules (melanin) of variable size and shape. In addition, melanosarcomas are often comprised of cells of two shapes—spindle-shaped and round to oval (epithelioid). Fibrosarcoma, hemangiosarcoma, and liposarcoma may be indistinguishable cytologically. All are comprised of basically spindle-shaped cells. Aspirates from hemangiosarcoma usually contain considerably more blood than the other sarcomatous masses. Liposarcoma cells may contain large lipid-filled vacuoles which may be demonstrated with lipid stains such as oil red O or the Sudan stains. Illustrations of the various sarcoma cells can be found elsewhere.

The discrete cell neoplasms constitute a rather large group of tumors of veterinary importance. Included among the discrete cell neoplasms are malignant lymphomas, mast cell tumors histiocytomas, and transmissible veneral tumors. Structurally, discrete cell neoplasms are seen cytologically as neoplasms comprised of individual round or oval cells with no adherence between cells and no ordered arrangement of cells (such as cluster formation). The individual discrete cell neoplasms have distinguishing features, which have been illustrated and described elsewhere.

CYTOLOGY OF BONE MARROW

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Throughout adult life, all blood cell types are continuously produced from primitive stem cells within extravascular spaces of bone marrow in mammals. Pluripotent hematopoietic stem cells produce pluripotent myeloid progenitor cells, as well as a pluripotent lymphoid progenitor cells. The pluripotent lymphoid progenitor cell gives rise to B lymphocytes, T lymphocytes, natural killer (NK) cells, and lymphoid dendritic cells. Lymphoid cells are also produced within peripheral lymphoid organs. The pluripotent myeloid progenitor cell gives rise to a series of progressively more differentiated progenitor cells that support the production of all non-lymphoid blood cells and some tissues cells (macrophages, myeloid dendritic cells, osteoclasts, and mast cells).

Blood cell production occurs in bone marrow of adult animals because of the unique microenvironment present there. Production of blood cells also requires the presence of specific hematopoietic growth factors that may be produced locally in the bone marrow or produced by peripheral tissues and transported to the marrow via the blood (humoral transport). Changes in growth factor production and/or the marrow microenvironment can have profound effects on blood cell production.

REASONS FOR BONE MARROW EXAMINATION

Bone marrow evaluation is indicated when peripheral blood abnormalities are detected that cannot be explained. The most common indications are persistent neutropenia, unexplained thrombocytopenia, and/or poorly regenerative anemia. The presence of multiple cytopenias indicates the likelihood of bone marrow pathology. Examples of proliferative abnormalities where bone marrow examination may be indicated include persistent thrombocytosis or leukocytosis (especially lymphocytosis), abnormal blood cell morphology, or the unexplained presence of immature cells in blood (eg, nucleated erythroid cells in the absence of polychromasia or a neutrophilic left shift in the absence of inflammation).

Bone marrow is sometimes examined to stage a neoplastic condition (lymphomas and mast cell tumors), estimate the adequacy of body iron stores, evaluate lytic bone lesions, and search for occult disease in animals with fever of unknown origin, unexplained weight loss and unexplained malaise. Bone marrow examination can also be useful in determining the cause of a hyperproteinemia when it occurs secondarily to multiple myeloma, lymphoma, leishmaniasis and systemic fungal diseases. It may also reveal the cause of a hypercalcemia when associated with lymphoid neoplasms, multiple myeloma or metastatic neoplasms to bone.

There are few contraindications for a bone marrow aspiration biopsy. Restraint, sedation, and anesthesia (when used) generally provide more risks to the patient than the biopsy procedure itself. Postbiopsy hemorrhage is a potential complication in patients with hemostatic diatheses, but it rarely occurs. Hemorrhage may occur after the biopsy of animals with monoclonal hyperglobulinemias, but it is easily controlled by placing a suture in the skin incision and applying pressure over the biopsy site. Postbiopsy infection is also a potential complication, but it is highly unlikely if proper techniques are used.

SMEAR PREPARATION AND STAINING

It is important for accurate bone marrow evaluation that smears contain marrow particles (stroma and associated cells). Marrow particles appear as small white grains in aspirates. One useful method to assist in the separation of particles from contaminating blood involves the forcible expulsion of several drops of the marrow aspirate onto one end of a glass slide that is then held vertically. Particles tend to stick to the slide while blood runs off. A second glass slide is placed across the area of particle adherence perpendicular to the first slide and, after marrow spreads between the slides, they are pulled apart in the horizontal plane. Resultant smears are rapidly air dried. Since marrow clots rapidly, one may collect marrow into a syringe that contains several drops of 4% EDTA as an anticoagulant. Marrow is mixed with the anticoagulant and expelled into a weighing dish or petri dish. Particles are then collected by capillary tube or pipette, and squash preparations are made.

Smears are stained with a Romanowsky-type blood stain such as Wright, Giemsa or a combination thereof. Satisfactory results can usually be obtained with the Diff-Quik stain, a rapid modified Wright stain. If adequate smears are available, one smear should be stained using the Prussian blue procedure for iron. Additional special stains may be needed to help differentiate the type of leukemia when present.

BONE MARROW ASPIRATE CYTOLOGY

Bone marrow should be examined and findings recorded in a systematic manner. Smears should be scanned with low-power objectives to gain an appreciation of overall cellularity and determine the adequacy of megakaryocyte numbers. Normal marrow appears heterogenous. As a general rule, erythroid precursors are smaller, have more nearly spherical nuclei with more condensed nuclear chromatin, and have darker cytoplasm than do granulocyte precursors at similar maturation stages. Rubriblasts have deeper basophilic cytoplasm than do myeloblasts, promyelocytes or myelocytes. Consequently, smaller and darker cells, observed by scanning marrow smears at low power, are usually erythroid precursors (unless lymphocytes are increased in numbers) and the larger, paler cells are usually granulocyte precursors.

Complete differential cell counts are not usually done on marrow smears, but rather a number of judgments are made and recorded as presented below.

The cellularity of the marrow is estimated by examining the proportion of cells versus fat present in particles. Marrow particles appear as blue-staining areas when viewed grossly. When examined microscopically, they contain vessels, reticular cells, macrophages, plasma cells, and blood cell precursors. Most particles in normal animals are composed of 1/3 to 2/3 cells. If few or no particles are present on smears, it is not possible to accurately estimate marrow cellularity.

The frequency and morphology of megakaryocytes should be evaluated. Most large particles should have associated megakaryocytes, and normally a majority of megakaryocytes are of the granular, mature type. Increased numbers of immature megakaryocytes or abnormal megakaryocyte morphology (eg, dwarf megakaryocytes) should be noted when present.

The distribution of granulocytic cells should be evaluated to determine whether the series is complete (ie, a normal number of mature granulocytes are present) and orderly. If there are increased proportions of cells in the proliferating pool (myeloblasts, progranulocytes, or myelocytes) compared to the later stages of development, this finding should be noted. Morphologic abnormalities, such as vacuolated cytoplasm, or increased representation of eosinophilic or basophilic series should be noted when present.

The maturation and morphology of the erythroid series should be evaluated to determine if it is complete (frequent polychromatophilic erythrocytes should be present) and orderly. Possible abnormal morphologic findings that should be noted include megaloblastic cells, frequent binucleate cells, and pleomorphic nuclei.

A myeloid to erythroid (M:E) ratio is calculated by examining 500 cells and determining the ratio of granulocytic cells (including mature granulocytes) to nucleated erythroid cells. The M:E ratio is generally between 0.75 and 2.5 in normal dogs and between 1 and 3 in normal cats. One needs to have a knowledge of the overall marrow cellularity, as well as the CBC, to interpret the M:E ratio.

Specific comments should be made about lymphocytes, plasma cells, osteoblasts, and osteoclasts when they appear in increased numbers and/or exhibit abnormal morphology. Normal marrow may contain up to 15% small lymphocytes and 2% plasma cells. Monocytes, macrophages and mitotic cells normally do not exceed 1% to 2% of total nucleated cells present. Osteoclasts and osteoblasts are rarely seen except in young, growing animals. Any abnormal cells such as mast cells, neoplastic cells, or macrophages containing phagocytized cells or infective agents should be described.

The amount of stainable iron present is routinely evaluated using the Prussian blue reaction. Stainable iron is easily found in normal marrow aspirates from most domestic mammals, so long as particles are present. It is decreased or absent in iron-deficient animals and increased in association with hemolytic anemias and the anemia of chronic disease. Normal cat bone marrow does not exhibit stainable iron, so its absence cannot be used to confirm a diagnosis of iron deficiency.

The final step in evaluating a bone marrow aspirate is to provide an interpretation of the cytologic findings in light of the history, clinical findings, CBC, and results from other diagnostic tests and procedures. For example, a high M:E ratio could indicate the presence of either increased granulocytic cells or decreased erythroid cells. Examination of CBC results from blood collected at the same time and an estimate of marrow cellularity usually allows the correct interpretation to be made.

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URINALYSIS FOR THE CLINICAL DETECTIVE

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COLLECTING URINE

When Should You Collect the Sample?

A urine sample should be collected for examination as part of the annual well-visit as well as anytime a diagnostic workup is done on a sick animal. If you are testing blood for some reason, you should probably test urine, too.

For urinary tract infection (UTI): Collect the sample for urinalysis and culture/sensitivity BEFORE starting antibiotic therapy (so the infection is not masked), and at least 3 days AFTER stopping therapy, to be sure the infection has been cleared. Remember that urine testing is the best way to screen for pyelonephritis in an anorexic or vomiting patient, since blood work or abdominal radiographs may not be that helpful to make the diagnosis. The leukesterase dipstick square too often shows a FALSE NEGATIVE, so you must do urine sediment exams! Dogs and cats with diabetes mellitus, hyperadrenocorticism, or on steroid therapy may have occult UTI without WBC in their sediment, so urine culture/sensitivity may be warranted in these patients even without seeing an active sediment. In animals prone to relapse or reinfection, check urinalysis and culture/sensitivity every 1 to 3 months after antibiotics are stopped.

To check if the animal can concentrate its urine: collect the sample BEFORE starting replacement fluid therapy, to see if the patient is able to concentrate the urine when it is in the partially dehydrated state. In an animal which is not dehydrated, first morning urine is usually the most concentrated urine of the day.

To check whether urinary acidifiers are working throughout the day, take a POST-prandial sample since that is the time of day the urine is most likely to be alkaline (see pH below) even in a carnivore, to see if the acidifier is working even then. To check whether urinary alkalinizers are working throughout the day, take a first morning (or fasted, PRE-prandial) sample, since that is the time of day when the urine is most likely to be acidic in a carnivore and you can check if the alkalinizer is working even at that time.

How Should you Collect the Urine Sample?

Cystocentesis samples are best for urine culture or when looking for evidence of infection in the sediment (bacteria, wbc), but the method is contraindicated if thrombocytopenia or bleeding tendency exists or if bladder cancer is suspected (in which case, a catheterized sample may be better). Cystocentesis is best done with ultrasound guidance if pyometra, prostatic abscess, or ascites is suspected. Catheterization may cause some trauma and if not done with care, increases the risk of introducing organisms into the bladder. Free catch (mid-stream) sampling is often adequate for urinalysis, E.R.D. (HESKA) or microalbuminuria (MA) test, urine protein/creatinine ratio, genetic metabolic screening, veterinary bladder tumor antigen test (V-TBA) and cytology, in other words, most situations except for culture (and possibly sediment, since preputial smegma or vaginal discharge may be misinterpreted as urinary tract infection). Sometimes it is worthwhile to compare free-catch samples to cystocentesis samples, to see if blood, WBC, or protein in a free catch sample may be due to lower genital excretion. Blood may be due to the method of collection. Cystocentesis, catheterization, and even manual expression of the bladder may cause bleeding.

The date, time of day, method of collection, observations concerning micturition, or other notables, such as “pre-fluids” or “pre-antibiotics” should be recorded. If the sample was taken off the floor, note it. The results may still be helpful for some things (USG, or if WBC or RBC are absent), but perhaps not for others, since contamination by disinfectant/cleansing agents from the floor, other exudations/dirt, may cause false results.

Where Should a Free-Catch Sample be Obtained?

If a free catch sample is deemed adequate for the intended test, should the owners try to get the sample from home, or should we get the sample once the animal gets to the hospital? I especially ask for the owner’s help if I want to see a first morning urine specific gravity, a fasted pH level, or if a urine cortisol/creatinine ratio will be done. A urine sample obtained during the hospital visit may show elevations of urine pH due to hyperventilation/anxiety or elevation of the urine cortisol/creatinine ratio due to stress.

Why Should You Do a Urinalysis?

A urinalysis gives additional information that you may not get from bloodwork, imaging, etc. For instance, a vomiting animal may have pyelonephritis or perhaps Fanconi syndrome (possibly genetic, eg, in Basenjis, or perhaps due to exposure to toxins, eg, found in chicken jerky treats in September 2007), and the blood work may be non-remarkable or non-specific. In the above examples, an active urinary sediment, possibly with WBC casts (pyelonephritis), or glycosuria in the face of euglycemia, respectively, will help make the diagnoses. There are many such examples where the urinalysis is a vital part of screening and ruling in/out differential diagnoses.

During a routine wellness examination, screening for proteinuria is recommended. See the 2004 ACVIM Consensus Statement on Proteinuria as well as “The Importance of Looking for Proteinuria” in these NAVC 2008 Proceedings. I recommend private practitioners use the in-house E.R.D. test or the quantitative MA test (Antech Reference Lab) for screening, and to switch over to a urine protein/creatinine ratio if the result is moderate or very high.

What Kinds of Tests Can You Do on Urine?

Besides urinalysis (urine specific gravity, dipstick, sediment), urinary protein testing (E.R.D.), microalbuminuria quantitation (MA), sulfosalicylic acid (SSA), urine protein/creatinine ratio, and urine culture/sensitivity, urine can be tested for many things that reflect the health of organs other than the urogenital system. In very small or anemic animals, getting more urine to test may be easier and safer than taking more blood to test. Urine tests may be a reflection of the health of organs other than the urogenital system, for instance pancreas (diabetes mellitus – glucosuria), adrenals (Addison's - urinary electrolytes; stress or hyperadrenocorticism – urine cortisol/creatinine ratio), liver (bilirubinuria, urine bile acid/creatinine ratio), etc. A urine metabolic screen may help diagnose a genetic abnormality or Fanconi syndrome. Cytology (cytospin examination) and the V-TBA are helpful to screen for neoplastic cells or antigens.

Who Should Do the Urinalysis?

YOU (or your staff) should do a urinalysis, in your facility, on a fresh urine sample, right away! Save some of the sample to send for confirmation of your findings by your outside reference lab. If you obtain the sample aseptically, put 1 to 2 mL in a culture tube for possible culture and sensitivity and use the rest for urinalysis, MA/E.R.D., possible urine protein/creatinine ratio, urine metabolic screen, etc. as appropriate for the case. If you have to refrigerate the sample before testing, be sure to allow it to come to room temperature before doing the dipstick examination.

GROSS URINE CHARACTERISTICS

Urine color, clarity, smell, and presence of flocculent material can all be important observations and must be noted. Observation of micturition for dysuria may be helpful, and if blood is grossly present, to note whether it is seen initially, at the end, or throughout the urine stream.

URINE SPECIFIC GRAVITY (USG)

The USG is normally read using a refractometer comparing the urine to water. Dogs and cats may dilute and concentrate urine over a wide range (dogs 1.001–1.070; cats 1.001–1.080). Consistently hyposthenuric, isosthenuric, or fixed USG <1.025 should be investigated. There are many causes of inability to concentrate urine, even when dehydrated. Caution must be used when considering renal disease versus Addison's disease, since both may present with a history of polyuria/polydipsia (PU/PD), vomiting, and azotemia.

URINE DIPSTICK READINGS

Dipsticks must be stored in their tightly capped bottle, away from light and air, and in-date. When used on either whole urine or supernatant, refrigerated urine should be allowed to reach room temperature, and each color square should be checked at the appropriate time listed on the bottle, under regular office (eg, fluorescent) lighting (not daylight). Some people have difficulty perceiving the subjective color changes; there are instruments (eg, Clinitek analyzers) that can report the dipstick chemical intensity more objectively.

In general, dilute urine may give false-negative (FN) results and high specific gravity or pigmented urine may give high or false-positive (FP) results. See Table 1 below for more FN and FP dipstick findings. Disinfectants with bleach or oxidizing agents may influence a number of squares. Some dipsticks have a square for USG, but it is not as accurate as a refractometer reading.

The dipstick for pH tests over the range of pH 5 to 9. Most carnivores eating a diet of meat protein will have fasting acidic urine. Due to post-prandial alkaline tide, the pH rises after eating in the blood and urine, even in carnivores. Dogs and cats eating a diet based on vegetable protein may have alkaline urine even when fasting. When an animal comes into the veterinarian's office, especially when excited during the trip or waiting room experience, hyperventilation will tend to cause respiratory alkalosis and urine pH may rise. Bacterial infection producing urease (*Proteus, Pseudomonas,* etc, which convert urea to ammonia) and old urine samples left out too long on the counter may cause urine pH to rise. *E. coli* infections may lower pH.

The protein dipstick square is not as sensitive or reliable as the ERD (HESKA) or MA tests. Alkaline urine tends to cause a falsely high reading on the protein dipstick square. Glucose in the urine does not necessarily mean the animal is diabetic. Blood glucose must be determined, since animals may have tubular defects due to UTI, necrosis, toxins, Fanconi syndrome, or primary glycosuria.

The square for blood picks up hemoglobin and myoglobin as well as intact RBCs. Speckling indicates a few RBCs. For diffuse color change, an examination of the gross urine, urinary supernatant, sediment, as well as serum color is helpful for complete interpretation. Myoglobinuria is pigmented, but myoglobinemia is not.

Bilirubinuria is conjugated (water soluble) bilirubin, and may be seen in normal dogs as well as dogs with hemolysis or liver problems. Bilirubinuria in cats is always abnormal and can be an early warning of problems even before hyperbilirubinemia is noted. The ketone square picks up acetoacetic acid but not acetone or beta-hydroxybutyric acid. The urobilinogen square is not that useful a tool in veterinary medicine.

Don't ignore a positive nitrite square. It may indicate a urinary tract infection with bacteria that convert nitrate (from the diet) to nitrite. This conversion requires urine to be retained in the bladder for at least 4 hours.

The leukesterase square is helpful when positive, but FN results in one study occurred in about 20% of cases with an active urine sediment. Always do a urine microscopic sediment exam as part of the urinalysis.

URINE SEDIMENT

Cells, crystals, casts, bacteria, sperm, parasites, neoplastic cells, etc. may be seen in the microscopic sediment examination. Some of these are normally present and should not be over-interpreted. Struvite crystals can be seen in normal urine samples, especially as the urine pH rises (see above for reasons for alkaline pH) or when the sediment droplet being examined begins to evaporate under the microscope's lamp. High pH and struvite crystalluria should not be treated as a problem in and of themselves. Oxalate and urate crystals may be seen in acidic or neutral urine in normal animals. Cystine crystalluria is abnormal, however.

Occult UTI may be missed in dogs with Cushing's, on exogenous steroids, or with diabetes, since WBCs may not marginate or become present in the urine sample. In these cases, urine culture needs to be done to rule out urinary infection.

Table 1. False Negative and False Positive Urinary Test Results

	USG	Prot	Glu	Blood	Bili	Ket	Uro	Nitr	Leuk
Dilute USG		FN	FN	FN	FN	FN	FN	FN	FN
High USG				FN				FN	FN
Low UpH		FN						FN	
High UpH		FP							
Pigmented urine		FP			FP	FP	FP	FP or FN	
Cold urine			FN	FN					
Old urine sample		FP		delay	FN	FN	FN	FN or FP	
Light (on urine)					FN				
Cleaning Agents, Disinfectants		FP	FP	FP					FP
Radiographic Contrast	Fhigh	FP or FN			FN				
Vitamin C			FN FP*	FN	FN			FN	FN
Antibiotics									
Penicillins		FN							
Cephalosporins									FN
Sulfas		FN			FP		FP		
Tetracyclines			FN						FN
Nitrofurantoin									FN
Gentocin									FN
Aspirin			FN						
BSP dye					FP	FP			
Formaldehyde			FN FP*	FN	FN		FN	FN	FN

Table Abbreviations:
Bili: bilirubin
BSP: bromsulfophthalein
FN: false negative result (dipstick)
FP: false positive result (dipstick)
FP*: false positive glucose result on a Clinitest tablet for reducing substances
Glu: glucose
Ket: ketones
Leuk: leukesterase square
Nitr: nitrite
Prot: protein
UpH: urine pH
Uro: urobilinogen
USG: urine specific gravity

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CHEMISTRY RATIOS FOR THE CLINICAL DETECTIVE

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Sometimes interpretation of a value on your clinical chemistry panel is made more meaningful when it is compared with other values. Certain variables may have particular relationships, either in the same direction with, or possibly diverging from, other parameters. Realizing these associations helps the astute clinical detective pick up warning flags which may be otherwise vague or easily missed. For instance, if an animal is dehydrated, it may have a pattern of changes, with values of Na^+, K^+, Cl^-, serum protein, and osmolarity above the normal range. If the animal also has pre-renal azotemia, the BUN and serum creatinine are also increased. If such an animal has a normal value for one of these parameters, for instance an unexpectedly normal value for K^+, and especially if the K^+ value is in the middle or lower end of the normal range, such a value is inconsistent with the entire picture, and the observant clinician would worry that the animal is actually whole body K^+ depleted and will likely need K^+ supplementation and monitoring, especially as intravenous fluids are given and the animal is rehydrated. Likewise, if an animal is dehydrated and has a serum albumin in the middle or lower end of the normal range, we may anticipate needs, that is, the possibility that with intravenous crystalloid therapy, the serum albumin may drop, the animal may be at risk for effusions or edema, and so we may want to prepare to monitor the animal for the potential need of colloid therapy, and we will be judicious in the quantity and rate of crystalloid therapy given. Thus, the clinician is at all times looking at the whole picture when presented with clinical data, including chemistry values, and looking at relationships and not just the numbers that are flagged with a star or an "H" or "L" for "high" and "low".

Laboratory values should be interpreted together, not as single events. What follows are some examples of the ratios that you may find helpful as a "clinical detective."

PCV/TS (PACKED CELL VOLUME/TOTAL SOLIDS)

This pair is really not a ratio, but it is a duo that is easily measured and recorded together, and is perhaps the earliest of blood test variables that the student learns to interpret together as a pair. These parameters are quickly assessed in emergency cases, and always important in any database. The PCV represents the bulk of the cellular components of the blood and is generally comparable to the hematocrit, red blood cell count, or the hemoglobin value. The TS is roughly comparable to the total protein of the plasma (although about 1 unit higher, since total protein is a subset of TS). These two variables (PCV/TS) may go up or down together, or they may diverge apart, giving important information in any situation and in any direction.

If the PCV and TS are both normal, you might think all is well. That is unless of course the animal is dehydrated, in which case perhaps rehydration will unmask anemia and hypoproteinemia. If both PCV and TS are elevated, the most common interpretation is that the volume of crystalloid in the blood is decreased (as in dehydration). If PCV and TS are both decreased, perhaps there is increased crystalloid in the blood volume compared with the blood constituents, possibly due to loss of both cells and protein after hemorrhage (blood loss), or in the case of aggressive overhydration (iatrogenic) with crystalloid therapy, or very rarely, the syndrome of inappropriate ADH secretion, which causes the animal to retain free water. The relationship may be further out of kilter as in these examples:

PCV normal with high TS:

1. The patient may be dehydrated and when rehydrated, anemia will be evident
2. The patient may have hyperglobulinemia (or less likely, hyperalbuminemia)

PCV high with normal TS:

1. The patient may have polycythemia (primary or secondary)
2. The patient may be dehydrated and when rehydrated, hypoproteinemia will be evident

NA$^+$/K$^+$ (SODIUM/POTASSIUM)

Look at the extremes of the normal ranges for these electrolytes in your lab, and see what the ratio is if you divide the lowest normal Na^+ by the highest normal K^+, and if you divide the highest normal Na^+ by the lowest normal K^+. For many labs, the normal ratio of serum Na^+/K^+ is 28–35. You can see that just by changing one variable out of the normal range a little bit, you can get an abnormal ratio which shouldn't be ignored. In the face of dehydration, both values generally increase together. Often in gastrointestinal (GI) or renal disease, with loss of both electrolytes, they go down together, and the ratio stays normal (although it is important to treat for these abnormalities). When the Na^+/K^+ ratio is low, we think of possible Addison's disease and plan to begin an ACTH stimulation test as soon as possible. Of course there are other reasons for a low ratio, such as whipworms, renal failure, GI (especially colonic) disease, effusive disease, or falsely high potassium due to thrombocytosis or K^+ EDTA contamination. If the Na^+/K^+ ratio is high, we consider steroidal causes, especially Na^+ retention due to hyperaldosteronism, or abnormal gastrointestinal or renal loss of K^+ in the face of dehydration causing elevated Na^+.

BUN/CREATININE (BLOOD UREA NITROGEN/CREATININE)

Normally this ratio is roughly 20 (range 9–33). If you look at your normals for BUN and creatinine from your lab, and take the extremes of each to see what the range might be if the two were completely divergent, the range is too broad (3–43) to seem helpful, so I use 10–30 as a rough guideline for normal.

Both of these substances are present in the glomerular filtrate and excreted by the kidneys. When the animal is dehydrated or overhydrated, they generally move in the same direction and the ratio stays about the same. Exceptions include sudden acute renal azotemia, prerenal azotemia, or rupture in the urinary tract, when BUN may increase due to pre-renal factors more than the slower rise of creatinine. It is helpful to recall where these substances come from. Protein in the diet is digested by proteases in the gut and amino acids deaminated by bacterial flora producing ammonia. Ammonia then travels from the GI tract via the portal venous blood to the liver where the urea cycle converts it to urea (NH_2-NH_2, called blood urea nitrogen on our panel). BUN also comes from protein catabolism in the body. If the liver is diseased such that there is congenital or acquired shunting of portal venous blood away from the liver, or if there is a rare urea cycle enzyme deficiency, then urea will not be synthesized and BUN will be lower than expected, relative to the serum creatinine. If there is a high protein diet, urea would tend to be high. Creatinine on the other hand comes from muscle with a daily constant turnover. If the animal is muscle wasted, or a very young puppy without much muscle as yet, then there isn't as much creatinine circulating to excrete. On the other hand, a very muscle-bound athlete in an anabolic state may have a higher creatinine turnover. Let's see how the BUN/creatinine ratio may be impacted in these examples:

Low BUN/creatinine ratio (eg, <10):

1. liver disease
2. animal is eating a low protein diet
3. animal is very well-muscled, with increased muscle mass (anabolic)

High BUN/creatinine ratio (eg, >35):

1. animal is eating a high protein diet
2. GI bleeding, which is as if the animal is eating blood, which is a high protein meal
3. catabolic disease, increased protein breakdown in the body
4. low muscle mass, causing the creatinine to be lower than expected compared with the BUN
5. hypovolemia/pre-renal azotemia (which also predisposes to GI ulceration)

A/G RATIO (ALBUMIN/GLOBULIN)

Normally this ratio is roughly 1. Albumin is only made by the liver. Globulins are made in the liver as well as by immunocytes. Albumin is a much smaller molecule (MW 60,000) compared with large globulin molecules, so that more albumin than globulin would be lost through diseased glomeruli (eg, protein-losing nephropathy, PLN) or vasculitis, where the pore size for leakage is small, whereas both albumin and globulin are lost from diseased intestine, with a larger leakage pore size (eg, in protein-losing enteropathy, PLE). Disease of the GI tract would lose whole plasma (albumin and globulins) and possibly whole blood including rbc's (GI ulceration). By looking at the total protein as well as the relationship of albumin to globulin, we can start to sort out PLE, PLN, liver disease, etc. Here are some examples:

- Total protein is high with normal A/G ratio: dehydration
- Total protein is low with normal A/G ratio:
  - loss of albumin and globulin together due to hemorrhage, plasma protein loss (PLE), burns, or exudative effusions
  - overhydration, dilution
- Total protein is low or normal with low A/G ratio: low albumin due to liver disease or PLN
- Total protein is low or normal with high A/G ratio: low globulin due to immunodeficiency
- Total protein is high or normal with low A/G ratio: high globulin state (gammopathy)
- Total protein is high or normal with high A/G ratio: high albumin due to hepatoma (rare)

Other parameters which will help in the diagnosis of PLE and PLN are the serum cholesterol and the PCV. Dogs with PLN tend to have high cholesterol, whereas dogs with PLE tend to have low cholesterol. Dogs with both PLE and PLN may have normal cholesterol. Dogs with GI bleeding may first appear as those with PLE because of their low albumin and globulin levels, but check the PCV, since anemia with panhypoproteinemia suggests GI hemorrhage. Signs of iron deficiency on the CBC (microcytosis – low MCV, hypochromia – low MCHC) may help support hemorrhage as a cause of anemia. Dogs with liver disease may be complicated in that they may have low PCV due to chronic disease or GI hemorrhage, low albumin due to decreased production, panhypoproteinemia due to GI hemorrhage, and cholesterol may be low, normal, or high with liver disease. Other parameters, such as ALT, alkaline phosphatase, and bilirubin may then be helpful. Beyond the biochemical profile, other tests include urine testing for proteinuria, abdominal imaging, serum bile acids, fecal alpha-1-proteinase inhibitor, endoscopy/biopsy, etc. may be necessary to help differentiate PLE, PLN, liver disease, GI ulceration, etc.

ALK PHOS/ALT (SERUM ALKALINE PHOSPHATASE/SERUM ALANINE AMINOTRANSFERASE)

In general, the serum alkaline phosphatase and serum ALT can be checked to see if they are traveling together or alone. In dogs, if the Alk Phos is elevated alone or is much higher than the ALT rise, we suspect pituitary hyperadrenocorticism, adrenal tumor, or exogenous steroid administration (iatrogenic). In puppies, we usually see elevated Alk Phos by itself, due to the bone isoenzyme of Alk Phos from osteoblastic activity during growth. Later in life, bone cancer with osteoblastic activity may also cause Alk Phos to rise independently of ALT. In liver disease, the ALT and Alk Phos both go up together and the Alk Phos is generally not much higher than the ALT unless there is cholestasis without leakage (as seen with cirrhosis and few hepatocytes left to leak ALT, or infiltrative diseases such as lymphoma). In cholestatic situations, the serum and urine bilirubin are probably elevated. Bilirubin is generally normal in steroid-induced hepatopathy. Sometimes it is helpful to submit blood for Alk Phos isoenzyme analysis, to quantitate hepatic vs. steroid-induced vs. bone isoenzymes of Alk Phos.

ALT/AST (SERUM ALANINE AMINOTRANSFERASE/SERUM ASPARTATE AMINOTRANSFERASE)

These two transaminases are leakage enzymes and the values usually rise at around the same rate when due to liver disease. Since AST is not liver specific, if the AST rises without a similar rise in ALT, consider muscle damage or hemolysis. A CK (creatine kinase) assay will help check for muscle damage.

CA/PHOS or CA/P (CALCIUM/PHOSPHORUS)

These two variables often go separate ways, due to the law of mass action. When the calcium goes down, the phosphorus usually goes up, and vice versa. Consider these situations:

Low Ca/P ratio with low Ca and high Phos:
1. Hypocalcemia due to renal hyperparathyroidism
2. Nutritional hyperparathyroidism
3. Hypoparathyroidism

High Ca/P ratio with high Ca and low Phos:
1. Hypercalcemia due to lymphoma
2. Primary hyperparathyroidism

Normal Ca/P ratio with high Ca and high Phos:
1. Hypervitaminosis D
2. Adenomatous renal hyperparathyroidism with renal failure

NA/CI (SODIUM/CHLORIDE)

These electrolytes usually go up or down together, as in dehydration or GI losses. But if they are divergent, this clue may help you make your diagnosis! Consider these situations:

Na^+ is high, Cl^- is low:
1. Dehydration with possible GI loss of HCl (vomiting), as in metabolic alkalosis
2. Alkalosis

Na^+ is normal, Cl^- is high:
1. KBr administration (false high Cl^-)
2. Hyperchloremic metabolic acidosis as in renal tubular acidosis with loss of bicarbonate (check TCO2, blood gases, kidney parameters)
3. Acidosis

Other ratios of interest include the urinary ratios of protein/creatinine, cortisol/creatinine, bile acids/ creatinine, etc.

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PROTEINURIA: DON'T MISS IT

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Proteinuria is relatively easy to check for and is one of those potential "silent killer" markers that can be associated with simmering damage which might otherwise go unnoticed by even the most observant owner. If proteinuria continues unrecognized, a variety of clinical signs could occur down the road, including severe and dramatic signs, with less chance of reversal or stabilization and more risk of morbidity and mortality.

Checking for proteinuria should be part of the annual wellness examination in all dogs and cats. Here we briefly answer questions clinicians want answered: Why should we bother checking for proteinuria, how often should we check for it, and which test should we use?

WHY SHOULD WE BOTHER CHECKING FOR PROTEINURIA?

Large amounts of protein in the urine which are associated with glomerular disease can lead to the nephrotic syndrome which can cause serious sequellae including death, even before azotemia and signs of renal failure occur. Significant proteinuria may lead to hypoalbuminemia and loss of antithrombin III, with the attendant risk for effusions, edema, and thromboembolic events. Even small amounts of protein leaking into the glomerular filtrate may cause tubular damage further down the nephron, and eventually renal function may decline due to decreased renal reserve, leading to renal failure. Hypertension (another silent killer) can be either a cause or effect of renal disease, especially glomerular disease. If we detect proteinuria, it is a reminder to check the blood pressure measurement and potentially avoid target organ damage from hypertension, including changes to the eye (blindness due to retinal hemorrhage or detachment), cardiovascular system (hypertrophic cardiomyopathy, arteriosclerosis, epistaxis), kidney (nephrosclerosis), and/or cerebrovascular system (cerebrovascular accidents or "strokes"). Other underlying diseases causing proteinuria, such as lupus, amyloidosis, or infectious/inflammatory, neoplastic, or genetic diseases triggering immune-mediated glomerulonephritis or glomerulopathy, may be first recognized by detection of proteinuria, a warning flag to look further. And vice versa: animals with infections, cancer, or immune-mediated disease affecting other organs (eg, polyarthropathy, hemolytic anemia, thrombocytopenia, pemphigus, myositis, myasthenia gravis, etc) should be closely monitored for the development of proteinuria. Screening for occult proteinuria in breeding stock may help future generations avoid familial protein-losing nephropathy; screening non-breeding individuals of such predisposed breeds will help spot those that may benefit from early therapeutic intervention.

Hypertension

Systemic hypertension (from any cause) increases glomerular filtration pressure and may cause proteinuria. Currently in veterinary medicine, measuring blood pressure is not done as routinely or as easily as is screening for proteinuria. Whenever proteinuria is found, a blood pressure measurement and retinal examination should be done. If proteinuria screening were not included in the wellness exam, occult target organ damage from hypertension may be missed as well, and possibly progress unchecked until gross clinical signs of blindness, epistaxis, or neurologic signs could occur.

Some causes of systemic hypertension include renal disease (especially glomerular disease), adrenal disease (Cushing's, hyperaldosteronism, pheochromocytoma), and thyroid disease (hyperthyroidism in cats and hypothyroidism in dogs). Examples of iatrogenic hypertension include exogenous steroids, high dietary salt intake in the rare salt sensitive individual, and phenylpropanolamine (PPA) treatment for canine urinary incontinence. Blood pressure measurement and screening for proteinuria should be monitored in cases so treated.

Infectious Diseases May Trigger Immune-Mediated Glomerulonephritis

Infectious diseases may cause glomerulonephritis and proteinuria due to immune-mediated complex deposition in glomeruli. Glomerulonephritis may be caused by acute infections, for instance with Rocky Mountain Spotted Fever or adenovirus-1 (infectious canine hepatitis), or chronic immune stimulation and glomerular immune-complex deposition may occur in carriers of many other infections such as anaplasmosis, babesiosis, bacterial infections, bartonellosis, borreliosis (Lyme disease), brucellosis, dirofilariasis (heartworm), ehrlichiosis, FeLV/FIV, fungal infections, hepatozoonosis, leishmaniasis, mycoplasmosis, and others. Some of these diseases may also cause vasculitis, polyarthropathy (synovitis), meningitis, uveitis, endocarditis, and/or bone marrow damage or immune-mediated cytopenias, such as thrombocytopenia, anemia, and/or neutropenia. If an infectious disease is causing proteinuria and is allowed to progress, more damage to the kidney will be ongoing, leading potentially to nephrotic syndrome, hypertensive target organ damage, and/or renal failure. Animals found to have infectious disease should be checked for proteinuria, and vice versa (animals with proteinuria should be checked for infectious diseases in their area). The commonly used in-house screening test, SNAP-4Dx (IDEXX) for heartworm antigen and antibodies against *Borrelia* (Lyme), *Anaplasma*, and *Ehrlichia* may identify seropositive animals. It is very rewarding to be able to detect and treat occult proteinuria in seemingly normal asymptomatic animals at a time when early intervention may make a real impact.

Genetic Predisposition for Proteinuria in Some Breeds

In breeds with familial glomerulopathy or amyloidosis, if genetic marker tests are as yet unavailable, screening for proteinuria before the animal is bred (several times a year), or annually for non-breeding pets, is advocated by conscientious breed clubs. A cut-off for normal urine protein/creatinine ratio of less than 0.4 may be used, and higher values investigated as to cause (eg, rule out urinary tract infection, calculi, etc). Examples of breeds predisposed to proteinuria include Bernese Mountain Dog, Bull Mastiff, Bull Terrier, English Cocker Spaniel, Samoyed, Soft Coated Wheaten Terrier, Shar pei, and others. Breeds that are predisposed to Lyme nephritis may also be monitored more closely, including Labrador and Golden retrievers, and Shetland Sheepdogs.

HOW OFTEN SHOULD WE CHECK FOR PROTEINURIA?

The ACVIM Consensus Statement on Proteinuria[1] recommended that dogs and cats be checked annually, as part of their wellness exam. Urine testing is also an important part of the database for sick patients. If a patient is proteinuric, guidelines (see Table 1) are given as to monitoring (for magnitude, persistence, and trend), investigation (for localization and diagnostic workup for cause), and therapeutic intervention (specific, supportive, and symptomatic). Mild proteinuria should be monitored over time to study progression or stability, and to notice any trend. Moderate to severe proteinuria should be monitored even more closely as well as investigated with other testing, for instance, urine protein/creatinine ratio, blood pressure measurements, CBC, biochemical profile, urine culture/sensitivity, chest radiographs, abdominal ultrasound, serologic tests for infectious diseases in the area, and possible renal biopsy. These patients should also have intervention, including an angiotensin-converting enzyme (ACE) inhibitor, antithrombotic low dose of baby aspirin (if hypoalbuminemic), amlodipine (if still hypertensive despite ACE inhibitor therapy), omega-3 fatty acid supplementation, diet modifications, and possibly, anti-emetics, antacids, phosphate binders, immunosuppressants, colloid or crystalloid supportive therapy, etc.

All dogs which are seropositive for antibodies against *Ehrlichia*, *Anaplasma*, or Lyme should be checked for proteinuria. Whether or not they are treated with doxycycline (and the current consensus is that they do not all need to be treated), when should they be rechecked for proteinuria? Since the carrier state may not always be cleared even if they are treated, I recommend rechecking for proteinuria two to three times/year (not just annually) in these dogs.

WHICH TEST SHOULD WE USE?

Searching for protein in the urine by dipstick can give false negative or false positive results. The dipstick square showing shades of green can be misinterpreted because of ambient lighting conditions, outdated sticks, dipstick bottles left open, etc. Almost 10% of men have some form of colorblindness and may find reading the dipstick problematic. False positives may be due to alkaline urine (due to respiratory alkalosis in excited, hyperventilating dogs; post-prandial sampling; or an old urine sample left out on the counter too long), pigmenturia (which turns all dipstick squares darker), or a highly concentrated urine. False negatives can be seen with dilute urine and old sticks.

Microalbuminuria (MA) tests are now available and are more sensitive and specific than the urine dipstick for protein. The in-house test, E.R.D. (HESKA) can be used as a routine initial screening tool, or a microalbuminuria assay may be included with the full urinalysis by an outside reference laboratory (eg, Antech Diagnostic Laboratories). E.R.D. results are read as negative, low, medium, high, or very highly abnormal (in urine diluted to a 1.010 specific gravity), or MA may be quantitated per urine volume in mg/dL. Monitoring for persistence and following the trend is important for low or medium results. For high or very high E.R.D. results, I recommend switching over to the quantitative MA or urine protein/creatinine ratio (Up/c).

Urine protein levels are not seriously impacted by the presence of microscopic amounts of blood in the sample (commonly occurring with cystocentesis samples), however, urine samples which are grossly bloody will have increased protein levels which interfere with diagnostic interpretations.

The source of proteinuria needs to be localized (pre-renal, renal, post-renal). Infection, inflammation (calculi), or neoplasia of the lower tract (bladder, prostate, urethra, prepuce/vagina) is common and needs to be ruled out so that proteinuria is not misinterpreted as a glomerular leak. Examination of urinary sediment for evidence of inflammatory cells is important, since the urine dipstick square for leukesterase often gives false negative results.

Table 1 gives guidelines recommended by the ACVIM Consensus on Proteinuria using the Up/c quantitation method for proteinuria.

Table 1. Guidelines Recommended by the ACVIM Consensus on Proteinuria using the Up/c Quantitation Method for Proteinuria

	Non-Azotemic Dogs and Cats	**Azotemic Dogs**	**Azotemic Cats**
Monitor	Up/c ≥ 0.5	Up/c < 0.5	Up/c < 0.4
Investigate	Up/c ≥ 1.0	Up/c < 0.5	Up/c < 0.4
Intervene	Up/c ≥ 2.0**	Up/c ≥ 0.5	Up/c ≥ 0.4

**Some clinicians use a lower cut-off for intervention, eg, starting to use an ACE inhibitor when Up/c is ≥ 1.0.

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PAIN MANAGEMENT IN ORAL SURGERY

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The utilization of regional nerve blocks for oral surgery in dogs and cats is synonymous with quality patient care. This article details techniques that can be incorporated into the companion animal hospital dentistry service to maximize safety, care and comfort for patients undergoing oral surgical procedures. This discussion also suggests adopting less misleading names for the regional nerve blocks, relying on simple anatomical regions blocked rather than the traditional confusing nomenclature.

Detailed descriptions of regional and local nerve blocks commonly utilized to provide analgesia for oral surgery in veterinary patients have appeared in numerous publications. Complete analgesia to the targeted tissue and a reduction in the concentration of the inhalant anesthetic are two significant benefits of proper administration of local agents. Hypotension, bradycardia, and hypoventilation are complications that can be minimized by the use of local and regional blocks for oral surgery. Local blocks eliminate the perception of pain making surgical anesthetic depths unnecessary.

AGENTS

This author commonly uses lidocaine[a] and bupivicaine[b] combined in the same syringe for regional oral nerve blocks. Lidocaine is not desirable as a sole agent due to its limited effect post administration (1–2 hours). Bupivicaine requires administration much earlier in the anesthetic event than lidocaine in order to be effective prior to surgical tissue manipulation. These limitations can be minimized or eliminated by using them in combination. The quick onset of lidocaine coupled with bupivicaine's extended duration of effect (up to 8 hours[5]) make them a good choice for combined use in regional nerve blocks. The agents may be used with or without epinephrine.

Although rare, complications are possible with inadvertent systemic administration or systemic uptake of locally delivered local anesthetic agents. Central nervous system excitement including seizures followed by depression, apnea, severe cardiovascular compromise, dysrhythmias and hypotension are all possible. Direct toxicity to skeletal muscle and anaphylactic reactions are possible with local administration. The author has never experienced any of these complications at the doses recommended in this article.

A maximum dose of 1.0 mg/kg of each agent in combination in the same syringe is recommended. Care should be exercised, especially in smaller patients and cats, so that maximum doses are not exceeded. The ratio of lidocaine:bupivicaine is 1:4 when using concentrations of 2% and 0.5 %, respectively. The total volume used depends upon the size of the patient and the number of sites that require analgesia. The maximum number of sites would be four if the patient requires surgical manipulation in all four quadrants. Table 1 shows recommended infusion volumes per site based upon patient size. Please note that these volumes represent both agents mixed together. Table 2 shows a sample calculation for a 40-kg dog.

Table 1. Recommended infusion volumes per site of lidocaine:bupivicaine

	Weight	Infusion Volume
Feline/Small dog	Up to 6 kg	0.1–0.3 mL
Medium dog	6–25 kg	0.3–0.6 mL
Large dog	26–40kg	0.8–1.2 mL
Extra large dog	over 41 kg	1.4–1.6 mL

Table 2. Sample calculation for a regional nerve block for oral surgery for a 40 kg dog

Patient Size = 40 kg
Regional Blocks desired = 3
Lidocaine 2% = 20.0 mg/mL
Bupivicaine 0.5% = 5 mg/mL

Calculation:
1.0 mg/kg x 40.0 kg = 40 mg total patient dose of each

Calculation:
Volume infused = total patient dose divided by the concentration of the agent
Volume infused for lidocaine 2% = 40 mg divided by 20 mg/mL = 2.0 mL
Volume infused for bupivicaine 0.5% = 40 mg divided by 0.5 mg/mL = 8.0 mL

The total dose of both agents combined for administration in the same syringe is 10 mL. Therefore, 3.33 mL could be used for each site. However, the recommended volume to be infused from Table 1 for this size patient is only 0.8–1.2 mL, so you would not need to draw up the total volume.

Calculation:
3 sites at 1.2 mL per site = 3.6 mL
3.6 x 0.25 = 0.9 mL lidocaine
3.6 x 0.75 = 2.7 mL bupivicaine

Physiologic parameters will determine if the block is effective. If blood pressure, heart rate, and respiration rate increase with surgical manipulation the block either was not correctly placed or hasn't had the proper amount of time for onset (5 minutes). If enough time has elapsed to be comfortable that onset is not an issue the block may be repeated as long as the maximum total dose is not exceeded. It should be noted that the low pH of inflamed tissue will render local anesthetics less effective.

OPIATES

Based upon human research the use of local analgesics and opiates in combination provides extended duration of action. The addition of morphine[c] or buprenorphine[d] to a regional brachial plexus block for limb amputation demonstrated close to a twofold increase in duration of effect over patients receiving only bupivicaine in one study. A similar model was used in another study where researchers demonstrated that the addition of buprenorphine to the regional block provided significant increases in duration compared to giving the buprenorphine intramuscularly.[7]

The author currently ulitizes opiates in the lidocaine:bupivicaine mixture for procedures where increased duration of effect is desirable. Patients that are particularly difficult to medicate, either in the hospital or at home, may benefit from this combination. Also patients in which chronic pain states exist, as seen in canine or feline stomatitis, may make postoperative pain management challenging. Morphine may be used as a portion of the premedication protocol at 0.5 mg/kg IM 20 minutes prior to induction. One fourth of that same volume is added to the local mixture per site to be blocked. Hydromorphone[e] is administered at 0.1 mg/kg as a portion of the premedication protocol. One fourth of that same volume is also added to the local mixture per site to be blocked. Buprenorphine may also be used as a premedication at 0.015 mg/kg following the same volume recommendations for local infiltration as with the examples above. Morphine and hydromporphone are pure mu agonists and are preferred for management of severe pain. Buprenorphine is a partial mu agonist and is a good choice for mild to moderate pain. All three agents may be used in either species; however, pure mu agonists, in particular hydromorphone, are known to cause hyperthermia in cats. If pure mu agonists are used either locally or systemically in cats, temperature should be monitored during and up to 5 hours post procedure.[8]

EQUIPMENT

None of the regional nerve blocks for oral surgery in dogs and cats need any special equipment to employ. A tuberculin syringe with a 5/8-inch 25-gauge needle is used for patients 4 kg or less. Three or six mL syringes with 22- to 25-gauge ¾-inch needles are used for patients over 4 kg depending upon the volume to be infused. The correct dose of the desired agents is drawn. The needle is advanced to the desired location. Aspiration is performed to ensure that the needle is not in a vessel and the agent is dispersed. If one encounters a vessel the needle is redirected and aspiration repeated. Once extravascular placement is confirmed the agent is administered. Be careful not to advance the needle during injection to avoid inadvertent vessel penetration.

REGIONAL NERVE BLOCKS

Four regional nerve blocks are commonly utilized to provide local analgesia to the different regions of the oral cavity. These blocks have confusing nomenclature in that the block may refer to the region blocked or the actual nerve that is blocked. This discussion suggests simplification and clarification of nomenclature to describe the region affected rather than the nerve blocked.

Two blocks exist for the maxilla. The rostral maxillary infiltrates the infraorbital nerve prior to exiting the infraorbital canal. The caudal maxillary anesthetizes both the infraorbital nerve and pterygopalatine nerve caudal to the second maxillary molar. The regional mandibular blocks include two blocks as well. The caudal mandibular infiltrates the inferior alveolar nerve on the lingual aspect of the mandible prior to its entry into the mandibular canal. The rostral mandibular anesthetizes the inferior alveolar nerve within the mandibular canal via the mental foramen.

The regional nerve blocks for oral surgery are similar for the dog and the cat. Some anatomical differences do exist, however. Variations in the approach to cats will be described following the discussion of these four regional blocks for dogs. The proposed new names are followed by the often confusing traditional names of these blocks in parentheses.

ROSTRAL MAXILLARY (INFRAORBITAL) REGIONALBLOCK

The rostral maxillary block provides infiltration of the lidocaine/bupivicaine combination adjacent to the infraorbital nerve and the rostral maxillary alveolar nerve within the infraorbital canal. The latter leaves the inferior alveolar nerve within the canal to enter the incisivomaxillary foramen to innervate the canine and incisor teeth. In addition, the first three premolar teeth as well as the maxillary bone and surrounding soft tissue are affected. To perform this block, retract the lip dorsally. Palpate the infraorbital neurovascular bundle beneath the vestibular mucosa. This is a large cylindrical band that exits the infraorbital canal dorsal to the distal root of the maxillary third premolar. The thumb of one hand can be used to retract the bundle dorsally. With the opposite hand the needle is advanced close to the maxillary bone ventral to the retracted bundle in a rostral to caudal direction to a point just inside the canal. The needle should pass without engaging bone. If bone is encountered the needle is withdrawn slightly and redirected until it passes resistance free into the canal. Proper insertion can be confirmed by gentle lateral movement of the syringe whereby the needle will meet resistance with the lateral canal wall.

CAUDAL MAXILLARY (MAXILLARY) REGIONAL BLOCK

The caudal maxillary block allows infiltration of the local anesthetic combination adjacent to the infraorbital nerve and the pterygopalatine nerve caudal to the second maxillary molar. These nerves are branches of the maxillary nerve that supply sensory innervation to the maxilla. In addition to the structures affected by the infraorbital block it will anesthetize the caudal cheek teeth and associated bone and soft tissue. The soft palatal mucosa and hard palatal mucosa and bone will also be affected by this block. To perform this block the mouth is opened wide and the lips retracted caudally at the lateral commissure. The needle is directed in a dorsal direction immediately behind the central portion of the maxillary second molar tooth. Advancement of the needle need not be more than 2–4 mms depending upon patient size.

ROSTRAL MANDIBULAR (MENTAL) REGIONAL BLOCK

The rostral mandibular block infiltrates the rostral extent of the inferior alveolar nerve just before it exits the middle mental foramen. The structures anesthetized include the incisors, the canine and the first three premolars. The adjacent bone and soft tissue are also affected. The middle mental foramen is located about one third of the distance from the ventral border to the dorsal border of the mandible at the level of the mesial root of the second premolar. The landmark for infiltration is the mandibular labial frenulum. The frenulum is retracted ventrally. The needle is inserted at the rostral aspect of the frenulum and advanced along the mandibular bone to just enter the canal. If bone is encountered the needle should be backed out and redirected until the needle passes freely into the foramen. Placement can be confirmed by moving the syringe laterally to encounter the lateral aspect of the canal. The patient's jaw, rather than the alveolar mucosa, will move slightly if the needle is within the canal.

CAUDAL MANDIBULAR (INFERIOR ALVEOLAR) REGIONAL BLOCK

The caudal mandibular block is performed by infiltrating the inferior alveolar nerve prior to its entry into the mandibular foramen on the lingual aspect of the caudal mandibular body. The lateral canthus of the eye is the landmark for this block. An imaginary plumb line is drawn from the lateral canthus of the eye directly to the ventral mandible. The needle is inserted into the skin at the lingual aspect of the ventral mandible at this point. The needle is advanced along the bone following the imaginary plumb line to a point one third of the distance from the ventral to the dorsal mandible. The needle will now be in the vicinity of the mandibular foramen where the inferior alveolar nerve enters the mandibular canal. It is not critical to be exactly at the foramen. Radiographic dye studies indicate that the agent diffuses to encompass a large area around the point of infusion. This technique blocks all of the teeth of the mandible on the side of infiltration as well as the adjacent bone and soft tissue.

Although very uncommon, patients receiving an caudal mandibular nerve block have been known to traumatize their tongues by mastication in the postoperative period. Observation and proper recovery assistance during this period will eliminate this complication. Staff members monitoring the recovering patient should ensure visual confirmation that the tongue is not trapped between the carnassial teeth if the patient is recovered in lateral recumbency. Maintaining the patient in sternal recumbency precludes the tongue deviation expected when a patient is laterally recumbent.

FELINE ANATOMICAL DIFFERENCES

Anatomical differences between species require slight variations in technique when considering nerve blocks in cats. When performing the rostral maxillary (infraorbital) nerve block in cats the approach is the same as described in the dog; however, the infraorbital foramen is relatively more dorsal in the cat. Therefore needle should be inserted more dorsally and then advanced in a rostral to caudal direction into the infraorbital foramen. As in the dog, the needle should not engage bone and should pass directly into the foramen.

The infraorbital canal in cats is also much shorter and the foramen relatively larger than that found in the dog. Because the canal is only a few millimeters long administration of the agent into the canal also places it adjacent to the infraorbital and pterygopalatine nerves. This results in creating the same effect as the caudal maxillary nerve block in dogs. In this discussion it is suggested that the single nerve block for the cat maxilla be termed the *maxillary nerve block* since it is performed as is the rostral maxillary block in dogs but blocks the same region as the caudal maxillary block.

Cats have no mandibular first and second premolars; therefore, the middle mental foramen in the cat is located midway between the mandibular canine and third premolar. Only in very small cats is this foramen not accessible to needle placement for administration of the rostral mandibular block. If one encounters difficulty the caudal mandibular block may be used as an alternative.

CONCLUSION

Regional nerve blocks for oral surgery are valuable tools in enhancing patient safety intraoperatively and patient comfort postoperatively. They are easy to administer and require no special equipment to perform. Their use encourages quick return to normal mastication and continuation of normal food and water intake shortly after oral procedures. Incorporation of oral regional nerve blocks into the dentistry service is paramount in providing the best in patient care. Simplification and clarification of nomenclature should be considered to eliminate confusion between descriptions of actual anatomical regions and the nerves themselves.

PRODUCTS

[a] Lidocaine Hydrochloride 2%, Phoenix Scientific Corp, St Joseph, MO

[b] Bupivicaine 0.5 %, Abbott Laboratories, N Chicago, IL

[c] Morphine sulfate 15mg/ml, Baxter Health Care Corp, Deerfield, IL

[d] Buprenex, Reckitt & Colman, Wayne, NJ

[e] Hydromorphone' 2 mg/mL, Baxter Healthcare Corp, Deerfield, IL

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NONINVASIVE ORAL FRACTURE REPAIR

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Oral fracture repair in dogs and cats has traditionally taken many different forms. Pins, plates, screws, and external coaptation devices are all methods previously employed that are relatively invasive. Small dogs and cats and immature animals have very little bone volume to support the more invasive devices often resulting in failure. Noninvasive methods employing the teeth and using interdental wiring, orthodontic devices, composite and acrylic can bypass traditional invasive methods decreasing procedure time and ensuring a comfortable occlusion and rapid return to function.

PATIENT EVALUATION

Oral fractures are particularly painful. Pain management should be an immediate concern for all patients with oral fractures. Immediate assessment of patient status should take into consideration possible complications of administration of certain analgesics. For example, patients with concurrent ocular trauma and potential glaucoma should not be given morphine in that associated vomiting from this agent will result in and acute increase intraocular pressure. Opiates should be avoided or used with caution in patients with respiratory compromise due their potential for causing respiratory depression. Nonsteroidal anti-inflammatory drugs (NSAIDs) should not be used in patients with hypovolemia, dehydration, or renal compromise. The patient should be considered as a whole when choosing appropriate analgesics.

A minimum data base should include a thorough physical examination, CBC, chemistry profile, electrolytes, blood gas analysis, urinalysis, thoracic and abdominal radiography and an EKG. Total patient analysis is paramount prior to consideration for sedation and oral evaluation.

Following the evaluation of the minimum database disposition is made concerning safety for general anesthesia and gross and radiographic evaluation of the oral cavity. If the minimum data base suggests that anesthesia is contraindicated preparation is made to compensate the patient for critical issues delaying anesthesia until the appropriate time. If definitive treatment must be delayed a tape muzzle should be placed to minimize additional tissue trauma from movement unless respiratory distress or vomiting are more pressing concerns.

The oral examination under anesthesia should include careful intubation not only for inhalant administration but just as importantly for airway protection. Oral hemorrhage and vomiting are common with head trauma and could severely decompensate the patient if an airway is not immediately established upon induction. A careful thorough oral examination should include maxillary and mandibular bone palpation, visual examination for swellings and lacerations in and around the oral cavity and skull, open fractures, epistaxis, temporomandibular joint (TMJ) fractures and luxations, symphyseal fractures, tooth fractures, tooth luxations and avulsions, malocclusions and lingual trauma.

Full mouth dental radiography is indicated following a thorough oral evaluation. Detail obtained from dental radiography allows for detection of lesions not possible with conventional skull films. Oblique and ventrodorsal (VD) TMJ films are indicated if assessment indicates possible problems in this area.

MANDIBULAR FRACTURES

Fractures of the mandible are more common and often more challenging than maxillary fractures in both dogs and cats. Displacement may be significant especially if both mandibles are involved. When repairing mandibular fractures primary attention must be paid to occlusion. If the teeth are returned to proper occlusion with noninvasive techniques, fracture repair is simultaneously accomplished. A proper occlusion eliminates tooth on tooth or tooth on tissue trauma postoperatively that might compromise apposition. Occlusion cannon be assessed without extubation and bite evaluation. Therefore, it is often helpful to perform a pharyngostomy to reposition the endotracheal tube so that occlusion can be checked during and after repair.

FAVORABLE FRACTURES

Favorable fractures are mandibular fractures where the normal forces of opening and closing the mouth aid in apposition of the fracture ends. The fracture line in these cases runs from the rostroventral to the caudodorsal mandible. Normal digastricus muscle function pulls the rostral aspect of the mandible caudally when opening the mouth. Similarly the temporalis and masseter muscles act to pull the caudal mandible in a rostral direction when closing the mouth. Therefore, the both processes of opening and closing the mouth impose favorable forces to oppose fracture ends in this type of injury. These fractures are often repaired solely with the aid of an acrylic splint applied to the lingual aspect of the teeth as the jaws are brought into occlusion.

NONFAVORABLE FRACTURES

Nonfavorable fractures exist when opening and closing of the mouth provides distraction forces to the fracture ends. When a fracture line runs rostrodorsal to caudoventral the muscles of mastication instill an effect opposite that of favorable fractures. These fractures require additional stabilization with interdental wiring and acrylic stabilization. Traditional methods aimed at providing minimal invasiveness include interosseous wiring. This is seldom needed when wiring and acrylic with or without a tape muzzle are employed during healing. Suturing of soft tissue should be delayed until stabilization is achieved in case interosseous wiring is needed. If this is the case access can be achieved in part via the existing defect.

TEETH AS ANCHORS

Teeth within the fracture line should be salvaged if possible. Severe periodontal disease and/or endodontic disease that is preexisting may warrant extraction in come cases. Treatment of these teeth following fracture healing depends on the ability of the dentist to treat the tooth or the bone loss at the time of the fracture. This topic extends well beyond the scope of this manuscript. Veterinary dental texts provide extensive discussions on periodontal and endodontic therapy for teeth in general. In most cases fracture repair can be completed utilizing the techniques described here. At discharge referral can be scheduled with a veterinary dentist for follow-up care of the teeth involved in the fracture line or otherwise traumatized. It is very important that client communication with this topic is discussed. Pet owners should be notified that traumatized teeth will require follow-up visits with a specialist or qualified individual after discharge from fracture repair. Extraction or endodontic therapy is often indicated especially if the tooth or teeth in question are involved with the fracture line.

MAXILLARY FRACTURES

Maxillary fractures commonly require little in the form of rigid fixation Soft tissue apposition, tape muzzles and/or acrylic splints are all that is needed in most cases. Epistaxis is a common sequela to maxillary fractures and usually resolves shortly after surgical repair. Ventrodorsal intraoral dental radiography should be employed to check for intranasal bone fragments in cases of severe nasal or maxillary trauma with epistaxis. Removal of fragments will prevent sequestra leading to chronic bacterial rhinitis. This may be accomplished through a displaced palatal fracture site or through dorsal rhinotomy.

ORTHODONTIC DEVICES

Orthodontic massel chain and button configurations have the advantage of providing fixation but eliminating rigidity associated with splints and wires. This may be of special benefit in young patients where jaw growth is not complete to allow some flexibility to further growth. When used alone massel chain and button configurations should be used with tape muzzles and Elizabethan collars to prevent trauma and minimize jaw movement. Orthodontic devices can also be integrated into acrylic splints where additional rigidity is required. Creative application of button and chain configurations may stand alone or form the backbone of acrylic splints providing excellent rigidity eliminating the need for interdental wiring.

INTERDENTAL WIRING

Interdental wiring is a viable noninvasive technique that can be used with or without stabilization with acrylic. It involves placement of 24- to 26-gauge wire between teeth on either side of the fracture line. Wire is generally placed ventral to the cervical bulge at the mesial and distal aspects of the teeth. Anatomical variations may dictate that the wire be passed through the gingiva to establish purchase. Notching of the tooth with a small round carbide dental bur or the utilization of composite bonding to secure the wire to the tooth are also possible. Wiring techniques are described extensively in veterinary dental texts. The Stout multiple loop technique provides incorporation of two or more teeth on either side of the fracture line. The Ivy loop technique is similar but incorporates only one tooth on either side of the fracture line. For mandibular fractures the loops are tied on the lingual aspect to eliminate problems with occlusion from the maxillary teeth and to act to reinforce purchase of the acrylic. More extensive fractures may require additional techniques. The Risdon's wiring technique may be used in these instances.

ACRYLICS AND COMPOSITES

Acrylic splints provide a stand-alone stabilization technique for many cases of mandibular and maxillary fracture repair. Unfortunately bonding acrylic to teeth is a technique sensitive procedure. At no time can plaque or saliva contact the surface of the prepared tooth or the procedure may fail. Interdental wiring is used in many cases to provide stabilization and ensure incorporation of the splint into something other than the tooth surface. A unique alternative to increase bonding success involves the use of composite acrylic buttons as an anchor.[a] A composite orthodontic button and bracket system is used to accomplish this. A silicone mold on the end of a plastic wand is filled with a flowable composite to accomplish a slight positive meniscus. The mold is placed on a prepared area of the tooth and light cured to achieve bonding. The mold is pulled from the tooth and the button or bracket is left strongly adhered to the tooth surface providing a solid anchor for retention of the acrylic splint. One bracket or button is placed on each tooth to be incorporated in the acrylic. The following series of steps are utilized to manufacture an acrylic splint using this technique.

1. Thoroughly clean teeth. If interdental wiring is to be used as an adjunct to acrylic splint stabilization rather than composite buttons the wire should be placed after cleaning.
2. Flour pumice[b] should be used to thoroughly polish teeth and wire to remove plaque. Any plaque will retard the ability of the acrylic to adhere to the tooth. Fluoride containing pastes will interfere with material setup.
3. Acid etch[c] all tooth and wire surfaces that will come in contact with the acrylic for 30 seconds. The labial surface of the mandibular teeth and the vestibular (buccal) surface of the maxillary teeth are used to avoid occlusion issues. Thoroughly rinse the etchant and dry with an oil free air source.
4. Place a small amount of primer/bonding agent[d] on the tooth surface where buttons are to be placed following manufacturers directions specifically. Bonding agents vary considerably in details of placement.
5. Place flowable composite[e] into the mold, hold the mold against the tooth, light cure for the

recommended time period and pull the mold from the tooth. The author uses an accelerated light cured composite that cures in 5 seconds. As an alternative, fabrication of an anchor can be done without the mold system by adding sequential layers of composite to approximate a similar contour.

6. After the composite buttons have been placed the acrylic splint is applied using a chemical cure self mix acrylic. Cover the proper aspect of the tooth surface for the length of the splint being careful not to involve the gingiva. Ensure a proper occlusion and apposition of fracture ends as the acrylic dries. This is facilitated by preplacement of the endotracheal tube in the esophagostomy site.
7. Rough areas can be smoothed with Goldie[g] or other burs. Oral hygiene should be encouraged if possible to keep the splint free from food and debris. The device should be inspected at regular intervals to ensure that it is intact. Radiographs are taken at 6 weeks to ensure adequate callous formation. The device is removed and the teeth cleaned and polished.

TAPE MUZZLE

Tape muzzles can also be stand-alone treatments for cases of maxillary or mandibular fracture where minimal displacement is present. It may also be used as a salvage procedure to encourage fibrous union in cases where repair is not economically feasible or prognosis for bony union is guarded. This is the case in many bilateral pathologic mandibular fractures secondary to periodontal disease. Tape muzzles are widely utilized and their application described in numerous texts and therefore is not described here.

CONCLUSION

Classic invasive oral fracture repair techniques have led to inadvertent or careless impingement on oral structures including teeth, periodontal ligament, cementum and the mandibular canal and its contents. Young animals are particularly terrible candidates for plates, pins, screws and osseous wiring due to the lack of mandibular bone while teeth are maturing. Cats and small dogs also lack significant bone volume. Avoidance of these invasive techniques should be considered paramount in dogs and cats of all ages. Noninvasive techniques are available to provide excellent stabilization, maximizing patient comfort and minimizing complications. They should be strongly considered as techniques of choice in any mandibular or maxillary fracture in dogs and cats.

PRODUCTS

[a] Orthodontic Mold System, Fairfieild Orthodontics, (800-321-0331)

[b] Flour Pumice Henry Schein, Melville, NY, (800-872-4346)

[c] Acid Etch Henry Schein, Melville, NY (800-872-4346)

[d] Bond 1 - 5th Generation, Pentron Technologies, Wallingford, CT, (800-551-0283)

[e] Flow-it ALC, Pentron Technologies, Wallingford, CT, (800-551-0283)

[f] Maxitemp HP (900-1279), Henry Schein, Melville, NY (800-872-4346)

[g] Goldie Bur (252-6531), Webster, Sterling, MA (800-225-7911)

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SURGICAL EXTRACTIONS

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Although preserving teeth is our goal, extraction is often the best or only option. The decision to extract or preserve a tooth is frequently decided by the amount of homecare the owner is willing or can perform. This information must be discussed with the owner prior to the dental therapy in order for the oral surgeon to appropriately treat and minimize anesthesia time.

Extraction technique is based upon fundamental knowledge of tooth's shape, number of roots and attachment. As a reminder, the only three-rooted teeth in dogs are the upper fourth premolar and the first and second molars (Figure 1). The upper second and third premolars, the lower second, third and fourth premolars and the first and second molars have two roots. All of the upper and lower incisors, cuspids, first premolars and the lower third molars have only one root. In cats (Figure 2), the incisors and cuspids and the upper second premolars have one root; the lower third and fourth premolars, the upper third premolars and the first molars and have two roots. The only teeth with three roots are the upper fourth premolars. Occasionally, the upper second premolar of cats may be absent or have two or three roots.

Before performing the extraction, a radiograph of the tooth will help ascertain information about ankylosed or fragile roots or those that are dilacerated or have abnormal shape. Intraoral radiology is the easiest technique and will give the best detail without superimposition of teeth, but extraoral film may be utilized with additional manipulation of the pet.

Begin the extraction by severing the epithelial attachment at the level of the sulcus with a small scalpel blade or periosteal elevator (Figure 3). With multi-rooted teeth, the furcation should be located. Sectioning of the tooth with a crosscut taper fissure bur (Figure 4) on a high-speed handpiece should begin at the furcation and moved coronally using a brush-type stroke (Figures 5 and 6). This reduces the tooth to single-rooted portions which can be elevated by severing the periodontal ligament. The dental elevator or luxator of the appropriate size is inserted into the space between the root and the alveolar bone. My elevators of choice are the Winged® Elevators (Figure 7) that come in various sizes. The wings are used to severe the periodontal ligament as the instrument is circumferentially rotated around the root using steady, gentle pressure for 10 to 15 seconds to fatigue the ligaments and cause hemorrhage within the periodontal space. The elevator is pressed further apically along the root using a slow twisting action on the instrument while cradling the jaw with the opposite hand. Do not use too much force or a lever action of the elevator. After the loosening the root, the instrument may be pushed to the bottom of the alveolar socket to elevate the root out. Alternatively, the loosened root may be gently grasped with extraction forceps and removed with slight rotational force. If the root cannot be easily withdrawn with the forceps, then more elevation must be performed.

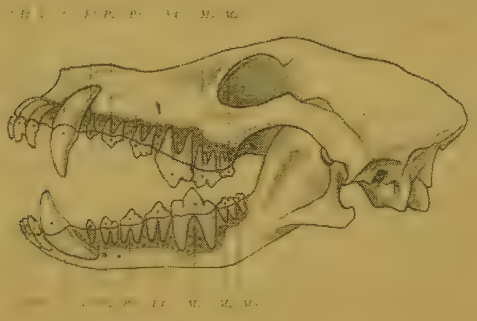


Figure 1. Canine dentition

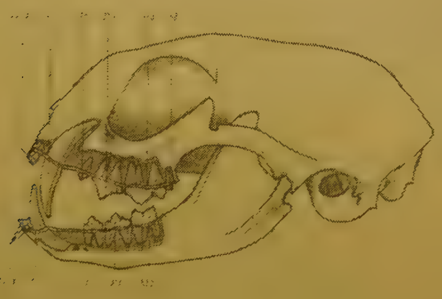
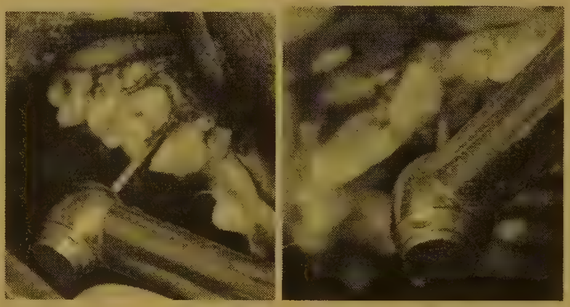


Figure 2. Feline dentition

Figure 3. Periosteal elevators.

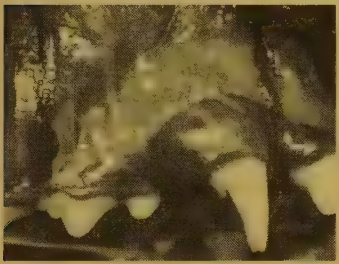
Figure 4.



Figures 5 and 6. Sectioning 108.

Figure 7. Winged dental elevators

Often times with more difficult extractions one must perform a full-thickness gingival flap and buccal bone removal. After severing the gingival epithelial attachment, two vertical releasing incisions are made on the mesial and distal aspects of the tooth. When removing upper canine (cuspid) teeth, I prefer to make my releasing incisions on the mesial aspect of the canine and the distal aspect of the 2nd premolar (Figure 8). Incisions must also be made in the interdental spaces between the canine and 1st premolar and the 1st and 2nd premolars. The larger flap provides better exposure of the jugal ridge without interference with the gingival tissue. Additionally, the suture lines will not be over a void in the bone. Elevation of the flap is accomplished with a periosteal elevator. The buccal bone covering the root is carefully removed using a round or pear-shaped bur (Figures 8 and 9) on a highspeed handpiece. After removal of the buccal bone from the alveolar margin to approximately ½ the length of the root (Figure 9), the tooth is gently elevated with appropriate size winged elevators or dental luxators on the mesial and distal surfaces to loosen the periodontal ligament (Figure 12).



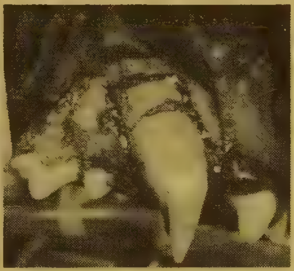
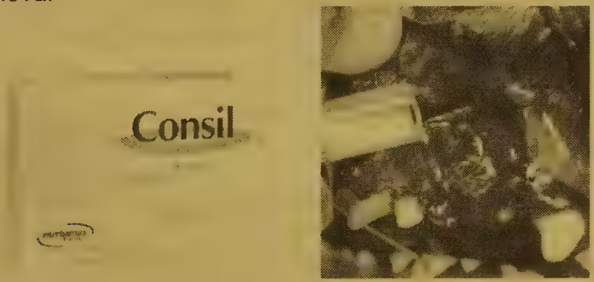


Figure 8. Releasing incisions. **Figure 9.** Buccal bone removal



Figures 10 and 11. Consil™ (Nutramax Labs) (*left*) and application of Consil (*right*).

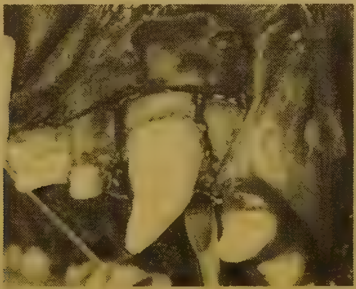


Figure 12. Elevation.

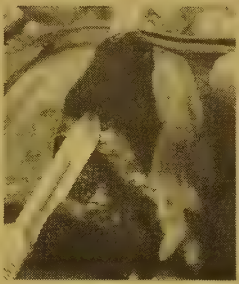


Figure 13. Flap-releasing incision

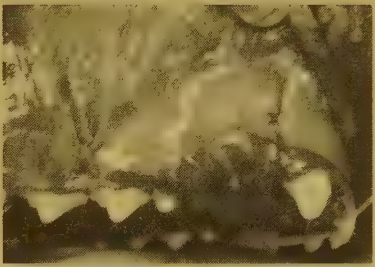


Figure 14. Final closure.

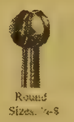


Figure 15.

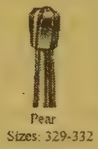


Figure 16.

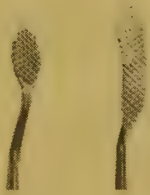


Figure 17. Bone files.

When removing the tooth from the socket, care must be taken to avoid causing an oronasal fistula by rotating the apex of the cuspid into the thin nasal bone. After the tooth is removed, there will be sharp, boney spicules along the alveolar margin. These should be removed with a crosscut bone file (Figure 17) or round bur. Extraction sites from infected teeth should have the soft alveolar socket cleaned of any granulation tissue that may be present at the apex of the socket.

Postoperative radiology should be performed to insure the removal of the entire root and to assess for any bone damage that might have occurred during extraction. Alveolar sockets tend to collapse or fill with soft tissue after tooth removal so the application of an osteogenic material, such as Consil™ (Figure 10 and 11), will help maintain the normal alveolar height. The gingival flap should be sutured to close the defect. Tension on the flap should be removed by passing a scalpel blade across the underside of the flap and severing the first layer of fibers near its attachment (Figure 13). Closure should be accomplished with an absorbable monofilament (not PDS) or braided suture material of appropriate size. Suture patterns may be simple interrupted, cruciate of vertical mattress (Figure 14). Postoperative homecare should include soft diet for a few days, pain medication, oral chlorhexadine rinse and antibiotics (if active infection is present).

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FELINE ORAL DISEASES

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PERIODONTAL DISEASE

Periodontal disease is one of the most common diagnoses made in veterinary medicine. A summation of the disease would be that bacteria ("plaque") accumulate on the surface of the teeth, gingival inflammation results, tissue destruction often follows if plaque accumulation is allowed to continue, and local and distant effects can be clinically significant.

Basic definitions that we need to understand are:

- **Dental Plaque***:* A "biofilm" consisting of bacteria, extracellular polysaccharides, cellular debris, leukocytes, macrophages, lipids, carbohydrates and salivary glycans. It attaches to the salivary glycoprotein pellicle that coats the teeth.
- **Dental Calculus (tartar):** Hard deposit often found on teeth, consisting of a mixture of calcium carbonate and calcium phosphate. Calculus is of little importance in absence of plaque. It provides a rough surface to harbor plaque.
- **Gingivitis**: Inflammation of the gingiva. It is considered "reversible": the inflammation disappears if the plaque is removed.
- **Periodontitis**: The destruction of periodontal attachment tissue (connective tissue and bone). This diagnosis is only confirmed when there is *radiographic* evidence of bone loss.
- Halitosis: The result of volatile sulfur compounds that originate from bacterial degradation of amino acids in plaque.

There are six stages of periodontal disease beginning with a healthy mouth and ending with exfoliation of teeth.

In Stage 0, the gingival tissues show no evidence of disease. The oral mucosa is coral pink or shrimp color and the attached gingiva will be firm, resilient and have normal stippling or orange-peel appearance.

In **Stage 1**, there is gingivitis with minimal inflammatory changes, minimal to no change in sulcus depth and up to 0.5 mm sulcus depth, usually due to gingival swelling and not attachment loss.

As the disease progresses to early periodontitis, or **Stage 2,** gingival edema and inflammation of the periodontal ligament occurs. Also, there is onset of crestal bone loss (<25% or <1 mm) and attachment loss with areas of root exposure due to gingival recession.

Untreated periodontal disease will next proceed to moderate periodontitis or **Stage 3.** This stage is characterized by moderate periodontal attachment loss and alveolar bone loss from 25% to 50%. Pocket depth or root exposure increases up to 2 mm. There will be slight tooth mobility.

Stage 4, or advanced periodontitis, is characterized by deep periodontal pockets and root exposure greater than 2 mm with alveolar bone loss greater than 50%. There is moderate to great tooth mobility. There can be extensive root exposure over the canine teeth or the maxillary alveolar bone may have a bulbous appearance around the canines which can progress to osteopenia and gradual extrusion of the canine teeth.

In **Stage 5,** we see exfoliation of teeth, healing of the empty alveolus, recession of inflammation, followed by atrophy of the dental ledge and smooth epithelium covering the gingival surface.

TOOTH RESORPTION (FELINE ODONTOCLASTIC RESORPTIVE LESIONS [FORL], FELINE NECK LESIONS, CERVICAL LINE LESIONS)

An extremely painful disease process seen in cats is odontoclastic resorptive lesions. Prevalence studies have shown that from as few as 20% up to 65% of domestic felines have this very painful condition.[5] Periodontal disease may or may not be present concurrently.

The lesions are classified according to the degree of involvement of the tooth. **Stage 1** lesions are early lesions extending less than 0.5 mm into the tooth's structure. **Stage 2** lesions have significant erosions which do not invade the endodontic system. When the lesion becomes deep erosion invading the endodontic system, it is classified as **Stage 3**. This is followed by **Stage 4** and is characterized as deep involvement causing loss of tooth integrity and more invasion of the endodontic system. Once the crown is lost and gingival overgrowth hides the irregular radiopacities of the roots, it is classified as **Stage 5**.

Stage 1 lesions are generally treated by applying a fluoride varnish to the teeth to desensitize and harden the enamel and to seal any exposed tubules. With **Stage 2** lesions, treatment consists of restoring the tooth with a glass ionomer and applying a fluoride varnish. Realistically **Stage 3 to 5** lesions result in extraction of affected teeth and the root fragments.

Some consideration of crown amputation and retention of root fragments of teeth that are resorbing has been presented. This is best summed up by the following statements:

- "On the basis of clinical, radiographic, and histologic findings of continued root resorption and absence of associated inflammation in teeth without endodontic or periodontal abnormalities, intentional root retention has been proposed as an alternative to whole-tooth extraction."
- "Teeth with endodontic disease or periodontitis and teeth in cats with gingivostomatitis or severe stomatitis should be removed completely."

LYMPHOCYTIC/PLASMACYTIC STOMATITIS (LPS)

Another oral disease of the feline that can cause much frustration is LPS. The etiology is unknown at this point, but bacteria, virus and immune status have all been implicated. This condition is chronic, nonresponsive to oral hygiene, antibiotics, anti-inflammatories, or immunomodulators. The breeds that are most commonly associated with this disease are Siamese, Abyssinian, Persian, Himalayan, Somali and Burmese. Some authors have seen no breed, sex or age predilections. Common presenting complaints of patients with LPS include ptyalism, halitosis, dysphagia, anorexia and weight loss. Clinical signs include hyperemia and ulcerative mucosa with a raspberry or cobblestone appearance. Diagnosis may be tentatively made on the basis of clinical features and lack of response to conventional oral hygiene treatment; however, biopsy is often needed to rule out neoplasia. Viral culture for calicivirus should also be done during the work-up, as this virus may be more important in the disease process than previously thought.

Treatment consists of elimination or control of the excessive inflammatory response by frequent and thorough professional prophylaxis for plaque control, antibiotics and anti-inflammatory drugs. Daily oral hygiene of the cat by the owner is also required. If the cat does not respond well to this treatment and is FELV and FIV negative, then immunosuppressive doses of anti-inflammatory drugs may be required. This may include a dose of 20 mg of methylprednisolone acetate given every 2 weeks for three to six treatments and then as needed. In severe or chronic cases, extraction of the premolars and molars (or all dentition in some cases) may be helpful in resolving the condition. The exception to this is in cats that are positive for calicivirus and have *no periodontal disease* of Stage 2 or greater.

In a study that looked at long-term follow-up of cases treated by dental extractions, it was shown that 60% of the cats were clinically cured, 20% had significant improvement, 13% had little improvement, and 7% had no improvement. These results beg to answer the question as to why are there such variation in results. Could it be that cats with plaque intolerance alone respond to removal of the teeth thereby removing the source of plaque while cats with no plaque intolerance (as evidenced by no periodontal disease of Stage 2 or greater) but carriers of calicivirus do not respond to the extraction procedure? Those cats with plaque intolerance and calicivirus may be the ones with marginal improvement. Food for thought!!

ORAL NEOPLASIA

Squamous cell carcinoma is the most common oral tumor in the cat. It can be either tonsillar or nontonsillar. The tumors are often proliferative, ulcerative, red and friable. It is most often seen in cats older than 10 years of age with no sex predilection. The lesion may resemble gingivitis or appear as a white or pink nodule with progressively mobile teeth due to bony destruction by the tumor. Radiographic bony changes are often seen at time of presentation. Wide surgical resection, in the form of mandibulectomy or maxillectomy, is effective only in early lesions. A poor prognosis is warranted, with only 50% of patients living beyond one year. Tonsillar SCC carries an even poorer prognosis due to its highly aggressive, extremely early rate of metastasis. Radiation has also been employed in selected cases.

Fibrosarcoma, the second most common oral neoplasm in cats, is usually found on the gingiva, palate or mucosal surfaces. It is also characterized by destructive local invasion, with frequent local recurrence and late metastasis

Other neoplasias that rarely occur in cats are malignant melanomas and osteosarcomas. Osteosarcoma of the maxilla and mandible is locally invasive but slow to metastasize, and might be curable with early detection and wide surgical resection. Although oral melanomas are rare in cats, they are as malignant as canine oral melanomas and carry a grave prognosis.

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PERRY DONTAL AND THE POCKET OF DOOM (ADVANCED PERIODONTAL THERAPY)

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Periodontal disease can vary greatly from patient to patient and even from tooth to tooth in the same mouth. From minimal inflammation and no attachment loss in Stage 1 periodontal disease to the beginnings of attachment loss (up to 25%) in Stage 2, then deeper pockets (up to 50% attachment loss) in Stage 3 and even compromised teeth (greater than 50% loss) in Stage 4, you must be able to tailor the treatment to the problem. Simple steps of a "prophylaxis" must sometimes be supplemented with additional periodontal management.

THERAPY GOALS

Then looking at periodontal disease, therapy is determined by a number of factors, such as the stage of the disease, and the desired outcome. There are several goals to set: (1) Removal of all debris or biofilm (plaque, calculus), (2) Saving the maximum amount of attached gingiva, (3) Minimizing attachment loss, (4) Minimizing pocket depth. Certainly, all foreign material, from bacteria to desquamated cells must be removed from the tooth surfaces and pockets in order to attain healing. Since the attached gingiva is the first line of defense against bacteria, a minimum of 2 to 3 mm is necessary to protect underlying tissues, as the looser alveolar mucosa doesn't afford that protection. The inability to halt attachment loss will eventually lead to tooth loss. Minimizing pocket depth is related to attachment loss, but is a more specific parameter, because pocket depth in itself directly affects the ability for effective home care and maintenance, and deeper pockets can harbor more virulent strains of bacteria. There are even times where excessive gingiva will be removed to decrease pocket depth (hyperplastic gingiva) or the gingiva will be sutured further down the root (apically repositioned flap) for the same effect. Attachment loss without pocket formation occurs when gingival tissue and bone is lost at the same time, exposing the roots and even furcation areas.

Intraoral radiographs are essential, in order to determine the extent and characteristics of bone loss. With recession of gingiva and bone across several roots and/or teeth, a horizontal bone loss pattern will often result in exposed roots. A deeper osseous loss down one root surface, an infrabony pocket may result from the vertical bone loss, and specific therapy may be needed to address that specific defect. These deeper pockets are more difficult to treat and maintain, and anaerobic infections may persist.

PERIODONTAL THERAPY

Periodontal therapy initially concerns itself with removing all plaque, calculus and debris possible. This is of particular importance if there is any attachment loss or pocket formation, because the surfaces must be thoroughly cleaned to help remove the destructive action of the bacteria and moderate the host response as well. Advanced procedures must be undertaken with commitment on the part of the owner as well, because regular home care and frequents follow-up visits will be important

The most effective way to minimize periodontal disease is to prevent it. The USDA has recently granted a conditional license to Pfizer Animal Health for a new product to be used as an aid in the prevention of periodontitis in dogs, as evidenced by a reduction in bone changes (osteolysis/osteosclerosis). This product is a *Porphyromonas denticanis-gulae-salivosa* bacterin, which can be administered to healthy dogs with two initial doses 3 weeks apart. A field safety study was conducted in over 600 dogs of multiple sizes and breeds, and safety was demonstrated in dogs as young as 7 weeks of age when vaccinated according to the label directions. A reasonable expectation of efficacy has been demonstrated in 8-month-old dogs. Duration of immunity for this product has not been evaluated; 6- and 12-month revaccination intervals are currently under evaluation in a field efficacy study. Consultation with a veterinarian is recommended. Additional efficacy and potency studies are in progress.

Practitioners need to evaluate each patient's risk factors for developing periodontal disease. Then they can evaluate the potential risks and benefits of a dental program including the Porphyromonas vaccine. The Porphyromonas vaccine is intended to be only one part of a complete dental program that includes examinations, cleanings and home care.

Supportive Care

Additional care beyond the periodontal work is often necessary to maximize the outcome. Assistance with various antimicrobial agents can help the patient fight off the bacterial onslaught, by using everything from oral rinses and gels to medically appropriate prescriptions of systemic oral antibiotics. Even pain management must be considered, because the conditions alone can be painful, and any surgical procedures must be covered as well.

Root Planing/ Subgingival Curettage

This is by far the most important aspect of periodontal therapy. If the debris is not thoroughly removed from the pocket depths, the disease will remain and intensify. The rounded tip of the curette and its rounded back, make it ideal for subgingival therapy, as opposed to the sharp tip and back of a hand scaler. While certain ultrasonic scalers are modified for subgingival treatments, most are not.

If root surfaces are exposed or if the pocket depth is less than five mm, closed root planing and subgingival curettage may be performed. Using a curette subgingivally with overlapping strokes in horizontal, vertical and oblique directions, root planing removes calculus, debris and necrotic cementum to provide a clean, smooth surface. The curette can also be angled slightly to engage the gingival surface for removal of diseased or microorganisminfiltrated tissues. When pocket depth exceeds 5 mm, or other pathology exists, more invasive procedures are warranted.

Perioceutic Therapy

In moderate pockets of up to 5 mm in depth (and generally deeper than 2 mm), once the area is debrided, placement of a local perioceutic gel containing doxycycline [Doxirobe™ gel (doxycycline hyclate)] can not only provide a direct antibacterial affect against any remaining bacteria, but the anticollagenase activity can help "rejuvenate" the soft tissue of the pocket. Doxirobe gel is not for use in dogs under one year of age, because the use of tetracycline during tooth development has been associated with permanent discoloring of teeth. Do not use in pregnant bitches, as the use of the product in breeding dogs has not been evaluated. The combination of the cleaning and therapy can often help reduce the pocket depth in moderate situations.

The two-syringe system is easily used, but requires some practice. When initially mixing the compounds, make sure the syringes are secure before mixing (100 passes). Once mixed, the material should be placed in syringe. A (place on end to get the most gel into syringe A before detaching) and a blunt tipped cannula placed. The tip of the cannula is gently placed to the depth of the treated pocket, and the material is slowly inserted into the pocket, until a small amount extrudes from underneath the gingival edge. By using light digital pressure on top of the gum, and by gently scraping the cannula tip on the tooth surface, the cannula can be removed without taking the gel with it.

The gel firms up on its own within a minute or two, or a drop of water can be placed on the material to speed up the process. Once firm, the visible material should be gently packed into the pocket, using an instrument such as a W-3, or beaver tail instrument. The owner should be instructed not to brush for about a week in the region (gels and solutions are recommended), nor to pick at the ridge of material that may become visible (light yellow-brown). The material is biodegradable and does not need removal.

Open Root Planing – Gingival Flap

When pocket depths exceed 4 mm but with minimal bone loss or diseased soft tissue that needs removal, a simple flap allows access and improved visibility for open curettage and root planing. Insert the scalpel blade into the sulcus and following the scalloped contour to sever the epithelial attachment. For large areas requiring treatment, vertical-releasing incisions can be made at the mesial and distal ends of the initial incision (at line angles of adjacent teeth). Using periosteal elevator, the gingiva is reflected to expose the root surfaces. A polishing of the root surfaces and irrigation with dilute chlorhexidine follows thorough root planing and subgingival curettage. After repositioning the flap, sometimes further apically down the roots, it is sutured interdentally with absorbable, interrupted sutures. While this procedure is most commonly performed on facial and lingual surfaces, deep pockets on the palatal aspect of the maxillary cuspid teeth can be exposed using a similar technique for treatment.

Reverse Bevel Flap

When the pockets are greater than 4 mm with bone loss and significant amounts of compromised pocket epithelium, a reverse bevel flap is employed to remove the affected gingiva and provide access for thorough cleaning, as long as sufficient attached gingiva is present. With the scalpel blade angled to the alveolar bone, the incision is made into the gingiva, leaving a thin collar of marginal tissue. The flap is elevated, sometimes exposing the alveolar crest, if osteoplasty is warranted. The collar of diseased tissue is removed with a curette, and the root surfaces are completely cleaned, polished and irrigated. Interdental sutures help reposition the gingiva.

Other periodontal procedures may involve pedicle or free gingival grafts to insure that at least 2 mm of attached gingiva is present at a particular site. Bone defect management and guided tissue regeneration strive to return the periodontal structures to a more normal state, and periodontal splinting allows stabilization of loose teeth to encourage reattachment.

GUIDED TISSUE REGENERATION

In an infrabony defect, where the attachment loss has formed a deep pocket in between the root and alveolar bone, inadequate therapy can lead to further attachment, and potentially tooth loss. Guided tissue regeneration (GTR) in dentistry normally deals with the reestablishment and regeneration of periodontal tissues lost due to disease or injury. Tissue regeneration has been demonstrated with alveolar bone, cementum, and the periodontal ligament in specific situations with specific therapies. Typically the soft tissues (gingival epithelium, gingival connective tissue) will grow back into a defect faster than the more important supportive tissues of the periodontium (alveolar bone, periodontal ligament).

A barrier between the instrumented root surface and the gingival flap, can act as a deterrent to exclude the gingival epithelium or gingival connective tissue from populating the root structure. This barrier then provides an area for the progenitor cells of the periodontal ligament and/or alveolar bone to have free access for migration. Because bone develops more slowly than the soft tissue of the periodontal ligament, the ligament should develop first, followed by bony incursion. It is generally believed that periodontal cells have the greatest potential to promote new attachment, but that bone also plays a significant role.

While some barriers are actual membranes, bulk material can also be placed to keep the soft tissue out. When a substance that promotes osseous growth is placed in the infrabony pocket, alveolar bone stands a better chance of filling the defect. There are even products that stimulate periodontal ligament re-growth.

An essential key to such a procedure is adequate exposure and debridement of the area. A gingival flap is necessary to allow for thorough curettage of all material in the infrabony pocket in between the tooth and root, including the removal of any granulation tissue. Once healthy bone and tooth surfaces are clean, the bio-synthetic glass particulate matter is packed into the defect, and the gingival sutured closed.

Postoperatively vigorous home care and plaque control is essential. Antibiotics for up to three weeks post surgically are recommended. Doxycycline is considered a good choice in human medicine because of its antibacterial and anticollagenolytic effects, thus aiding to stabilize collagen locally.[6] Nonabsorbable membranes are normally removed one to nine months following surgery. Materials such as Consil™ (Nutramax Labs) do not need removal.

The entire staff plays an important role in home care. Staff members should be well-versed in available home care products and techniques, so they can aid in demonstrations for the pet owner. Client education can start at a very early stage, introducing new puppy and kitten owners to the concept of brushing as part of a regular grooming and hygiene program. Some pets may be difficult to treat, and the risk of injury to the owner should not be assessed in recommending home care. It is important to make sure from the start that the commitment is there for the advanced procedures.

Equipment

Many standard pieces of equipment and supplies can be used, including scalpel blades (15C works well), scissors (sharp/sharp for gingival remodeling), and sutures (usually absorbable, from 3-0 to 5-0). Full evaluation is not possible without the use of a periodontal probe/explorer to ascertain pocket depths, and intraoral radiography is essential to get a complete picture of the situation, whether there is periodontal bone loss or for pre-extraction (and post-) radiographs. Other essential tools include periodontal curettes for scaling root surfaces, periosteal elevators (Molt No. 2 or No.4) for elevating gingiva, good elevators (winged elevators are especially helpful), and some means of sectioning teeth.

Refining Your Skills

Periodontal surgery. While most practitioners provide dental services to their patients, they seldom cut the gingiva to provide sufficient exposure for adequate treatment. Opening gingival flaps takes little additional skill, just the ability to know where to make the flap and proper tissue handling technique. In pockets less than 5mm, a periodontal curette, with its round toe and rounded back, is very useful for closed root planing and subgingival curettage where no flap is needed.

Any time a periodontal pocket is deeper than 5 mm, the area must be exposed for adequate cleaning. With the periosteal elevator, an envelope flap can be made by lifting the gingiva directly over the defect, and extending it the distance of 1 to 2 teeth on either side to provide enough exposure. This can stretch the tissue out significantly if the pocket is deep, or the area is too wide. Therefore, a flap can be created by making diverging incisions mesially and distally to the defect, through the attached gingiva past the mucogingival line into the alveolar mucosa. The periosteal elevator is then used to lift the flap off the alveolar bone, providing access to the site. Sufficiently elevate for adequate exposure, but don't expose any more bone than is necessary.

Once the site is laid open, every effort must be made to clean out all debris and granulation tissue from the pocket, particularly in pockets that extend down the root of the tooth, in between the tooth and alveolar bone (infrabony pocket - vertical bone loss). Once cleaned, material such as Consil can be used to help promote osseous healing and discourage soft tissue growth into the area. This form of therapy (guided tissue regeneration) can be of particular importance with deep pockets at the palatal aspect of maxillary canines, and with deep infrabony pockets involving the lower first molar that can compromise mandibular strength. While the lower first molar defects can often be exposed using standard releasing incision flaps, the deep palatal pockets provide additional challenges. It is essential in this area to design a flap and plan sutures that will bring the gingival margins snugly against the tooth, to protect the materials in the pocket. Mesial and distal releasing incisions can be made extending out from the canine towards the adjacent teeth, on the gingival papillae. Exposure with this method can be somewhat limited, like an envelope flap, and closure involves using a sling suture technique, running the suture in a semi-circle pattern within the palatal mucosa from a mesial to distal direction. Then exiting distal to the canine and re-entering near the same site, reversing the semi-circle pattern to exit mesial to the tooth. Finally tying off the two ends which tightens the flap against the tooth. Incisions made directly into the palatal mucosa not only can cut the palatine artery, but make a flap that is more difficult to hold against the canine.

An alternate method is making a crescent-shaped flap in the palatal mucosa, extending from a point just mesial to the canine in the incisor-canine interdental space, and running medial to the canine to a point just distal to it. When the flap is elevated, there will be hemorrhage from the rostral severing of the palatine artery, but it can be tied off at that extent and preserved within the flap itself. Once elevated, good exposure allows for thorough cleaning of the infrabony pocket. Exercise to avoid puncturing the remaining alveolar bone separating the pocket from the nasal cavity (oronasal fistulation), or the tooth will need to be extracted. Once the pocket is cleaned and filled, simple interrupted sutures can hold the crescent flap in place.

If some gaps appear, a small amount of the mesial extent of the flap can be trimmed, to bring the gingival margin closer to the tooth. Sutures can be placed to join the cut edge of the flap back to the palatal mucosa, as long as no tension is placed on the flap that would cause it to pull away from the tooth. A small gap between the cut edge of the flap and the remaining palatal mucosa will typically heal without complication.

In some areas there will be horizontal bone loss and suprabony pockets (bone loss occurs at same level of attachment loss but no defect in between the tooth and alveolar pocket). Once the area is exposed, all root surfaces areas should be thoroughly cleaned using curettes. In some cases, if the bone loss includes interdental spaces, the flap can be sutured in place so the gingival margin is actually placed further down the root than originally positioned (apically repositioned flap). This can help minimize the pocket depth, though the actual level of attachment is still the same, just more root structure is left exposed. These sites are not amenable to osseopromotive products.

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INTRAORAL RADIOLOGY STANDARD OF PRACTICE

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Intraoral radiology may have once been considered a special service or luxury, but as practices continue to offer expanded dental services, this means of diagnosis is a vital tool assisting in the diagnosis, treatment planning, and monitoring of oral disease.[1] Diagnostically, being able to assess normal anatomy helps to determine if abnormalities exist, including variations in development (missing or aberrant teeth) or acquired diseases that may affect the bone and tooth structure (cranial mandibular osteopathy or CMO, hyperparathyroidism, neoplasia).[2] When determining the possible treatment for problems such as feline resorptive lesions, endodontically compromised teeth, and periodontal disease, radiology can help the practitioner make a more accurate assessment. Preoperative radiographs can help monitor extractions by revealing abnormal root structures, impacted teeth, and ankylosed roots. Postoperative films check treatment success. Endodontics requires several films during the procedure to evaluate routine treatment and reveal complications.

EQUIPMENT

Films

For dental films, extraoral non-screen as well as panoramic products may be used, but for greatest versatility, the smaller, non-screen intraoral films are most useful. Occlusal films (No.4, DF50 or EO41) are 2 1/4 X 3 inches in size and often used for imaging the incisal areas, both mandibular and maxillary and larger cuspid teeth. Due to restrictions of the palatal vault or intermandibular space, smaller films can be placed more readily to radiograph premolars and molars. The periapical films (No. 0 – EP01, No. 1 – EP-11 and No. 2 – EP-21) range from 7/8" x 1 3/8" to 1 1/4" x 1 5/8". Proper placement of the film packet with accurate positioning technique can provide isolation of a specific tooth with excellent detail. This detail is enhanced by the fact that intraoral film is non-screen, double-coated emulsion film. A raised dot imprinted on the film and packet indicate the side that should face the x-ray tube, placing the concave "dimple" away from the tube. Once developed, this dot helps determine the orientation and identification of the teeth. The film is encased in an inner black paper sheet with a layer of lead foil on the backside that reduces backscatter from deeper oral tissues, all in a plastic or paper cover. The flexible films may be held in the mouth by just closing the occlusion, or with the help of plastic holders, hemostats, rubber bands, or malleable materials (modeling clay) in plastic bags. Most digital radiographic sensors are similar to a size No. 2 film though smaller ones are currently available, and a sensor similar in size to the #4 films is being developed.

Radiographic Unit

As a veterinarian's dental skills improve and he or she begins to perform more advanced procedures such as endodontics, radiology increases in importance. To facilitate the use of radiology, a dental x-ray not only will prove to be invaluable, but will often help the practice financially, with increased use. If you can place the smaller dental unit near the area where procedures will be performed, that greatly enhances its convenience. The maneuverability of the x-ray head facilitates angulation for positioning techniques. The position indicating device (PID) or cone may vary, depending on the machine. Most units produced for veterinary use have customized dental 'map', so the region or tooth being imaged can be selected for appropriate exposure time (most have a set KVP of 70). The "F" number may need adjusting, depending on the intensity of the individual unit's exposure or if the unit is to be used with a digital sensor. Digital sensors typically need a much shorter exposure time than typical intraoral films.

After appropriate installation, registration, and calibration, the extent of scatter can be determined, but is usually minimal 6 feet away from most dental radiographic units, as long as the area directly in the path of the beam is avoided. Appropriate protective measures for both operators and patients should be observed.

Although less convenient and more challenging to obtain diagnostic radiographs, intraoral films (D-speed/Ultraspeed; Kodak) can be used with a standard x-ray machine using a technique of 100 mA and a focal distance of 12 inches (1/10th to 1/15th second) or 36 inches (2/5th to 3/5th seconds). The KVP will vary from 65 for a cat or toy dog, 70 for a small dog, 75 for a medium dog, 80 for a large dog, and up to 85 KVP for a giant breed.[4] With these parameters as a general guide the practitioner for their specific equipment can develop an appropriate technique chart. With E-speed film (Ektaspeed, Kodak), the exposure time can usually be reduced by half. There is some loss of contrast and these films are not recommended for development in some chairside developers (check manufacturer's recommendations).

TECHNIQUE

The appropriate positioning of the film and beam is often the most challenging aspect of taking intraoral radiographs. Be sure to get good, practical instruction on taking radiographs once you have obtained a unit. It is often much easier to learn about positioning and making adjustments with a digital unit, as the image is immediately available for review, and any changes can be made as soon as the image is displayed.

While a parallel technique (film and object parallel and x-ray beam perpendicular to both) would be ideal to minimize distortion, most areas of the oral cavity do not lend themselves easily to this positioning. The only region where the film can be placed parallel to the teeth is that of the mandibular premolars and molars, with a corner of the film pressing into the intermandibular space. The most mesial (rostral) roots and teeth may not be visible on this view, as the film may be limited by the mandibular symphysis, but aiming the radiographic beam from a slightly rostral oblique position may allow these roots to be imaged.

For the rest of the teeth in the oral cavity, parallel positioning is not possible, so a film is placed as close to a parallel plane to the object (root or tooth) as possible. Remember to center the film on the region to be assessed, such as the alveolar bone ridge for assessment of periodontal bone loss. Note – if it looks like there might be periodontal bone loss, but some tooth structure is 'burned out" or dark, retake the radiograph using a slightly lower setting (shorter time). If the roots are to be imaged, be sure the film is positioned further towards the roots, not necessarily the crown.

Once placed, one option is to use a bisecting angle technique for these films by aiming the beam at a line that bisects the angle formed by the long axis of the object (tooth) and the film. Another way of determining beam position is to first line up the beam (or similar object such as a 2-inch roll of tape or tongue depressor) perpendicular to the film. This would result in an image that is too short (shadow of a tree at noon). Next, line up the beam perpendicular to the root (tooth); this image would be too long (shadow of a tree at daybreak). Then, split the difference between these two positions, and the resulting image will be approximately the same size as the object, thus minimizing the distortion (and the beam will be perpendicular to that bisecting line mentioned earlier). Helpful devices, such as connecting two tongue depressors with a brad, or even using the handles of a small pair of forceps, can help you visualize the two positions (perpendicular to film; perpendicular to tooth), so you can aim the beam halfway between the two. This perspective will also help you make appropriate adjustments to an image; if you want to make the image shorter, move the beam to a position more perpendicular to the film. This can be helpful when trying to image a long canine tooth or the roots of a large upper forth premolar on one film, by shortening the image on purpose.

One challenging site to radiograph can be the maxillary premolars in a cat. Even with using the above techniques, the shape of a feline head and position of the zygomatic arch can make it difficult to get a reasonable image of the premolars. The angles of the head of a cat may also result in tooth overlap, so you may start by visualizing what would be a 'straight-on' shot by looking through a two-inch roll of tape, and adjusting the beam from there. If the general positioning is adequate, but the zygomatic arch is still in the way, you can elongate the image on purpose (move the beam more perpendicular to the tooth), which will distort the teeth slightly, but may allow you to evaluate more of the roots.

An alternate method involves using a small mouth gag to prop the mouth open, with a towel underneath the cat's head. With a slight shift in the position of most cats' heads, you can adjust the arcade on the downside to the teeth are nearly parallel to the table surface. Then place the film underneath the head, towards the dorsal aspect of the head. In this position, aim the beam obliquely across the head in order to capture the image of the downside roots (picture where the beam will hit the roots, then the film, and make sure the film is positioned correctly), and take the film. If the upside maxillary premolars superimpose the downside premolars, the angle of the beam needs to be slightly increased. This extraoral technique can also be helpful when assessing the mandibular first premolars in dogs, and even the maxillary premolars in brachycephalic patients.

Each of these positions has been described for positioning with a dental radiographic unit with a mobile positioning arm. If a standard radiographic unit is to be used, the patient's head should be adjusted halfway in between the two positions that would have the beam aimed perpendicular to the film, and perpendicular to the tooth. Another way to look at this is if the film was parallel to the table (perpendicular to the beam), the image would be too short, and if the tooth root was parallel to the table, the image would be too long, so split the difference (see Radiographic Unit section above for techniques).

Extraoral studies may be used, both in parallel and bisecting techniques, for survey films, to assess massive oral injuries, fractures, neoplasia, or temporomandibular studies. However, in dealing with select structures and teeth, extraoral radiology often cannot provide sufficient detail or accuracy due to superimposition of structures or distortion. Intraoral films offer better dental isolation as well as the enhanced detail of non-screen film. The films are relatively inexpensive, and can be developed quickly in rapid dental developer/fixer solutions.

Film Development

If intraoral films are to be used, a chairside developer will facilitate development. The film packet is opened under appropriate light restrictions and the film placed in a film clip, either metal or plastic, or a hemostat. After immersing in water for 5 seconds to hydrate the emulsion, the film is place in the developer with initial agitation for 15 to 60 seconds (depending on solution and temperature). Following a water rinse, the film is then placed in the fixer solution with intermittent agitation for approximately twice the developing time. After a final water rinse, initial assessment can be made. The film holders may be suspended for drying or placed in a film drying stand. Film identification can be facilitated by the used of radiopaque ID numbers placed on the film before the exposure or with marking pens after drying. Films may be displayed in cardboard mounts, plastic mounts, or stored in dental envelopes

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FELINE PRURITUS – SCRATCH IT LIKE MAD!

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WHAT IS PRURITUS?

Pruritus is medical term derived from the Latin prurire meaning itch. Samuel Hafenreffer defined pruritus 340 years ago as "an unpleasant sensation provoking the desire to scratch." If you feel an itchy sensation, you scratch near it in order to change your perception of that sensation. Since our patients might rub, lick, scoot, chew, roll, or shake, as well as scratch, we must expand the definition. Indeed, the most common expression of pruritus for cats is obsessive grooming, not scratching. Just to be extra difficult, cats are notorious for exhibiting this behavior in front of owners, who never see them lick but present a cat with hair perfectly barbered off in beautiful symmetry.

Threshold

Pruritic mediators or sensations are not equal in their ability to elicit itch. If sensation exceeds threshold you itch, otherwise you don't. The same stimulus may or may not induce pruritus depending on the individual threshold and the circumstances that influence their threshold at that moment.

Modulation

Psychological state can raise or lower threshold. Activity or other stimulation can distract a patient from scratching without changing the pruritic mediators or sensation. When left alone an atopic cat may lick rhythmically for hours, but when the family comes home, another cat is introduced, or food is present, they stop grooming immediately. When the house becomes quiet and dark at night, the cat returns to licking or scratching. Some itch so intensely that no amount of stimulation or physical restraint distracts them. Parasites, herpes, and food allergy can stimulate self-mutilating pruritus. We can modulate psychological states to reduce pruritus by recommending environmental enrichment.

Summation

Multiple stimuli can add up to exceed threshold and worsen the severity of pruritus. For example, an atopic cat may not itch when exposed to ragweed pollen alone, but becomes pruritic when secondary factors such as dry skin, fleas, or bacterial infection are present. With secondary factors, patients may require high dose steroids to control pruritus. By preventing fleas and treating infection, pruritus is more easily managed with relatively safe drugs. A corollary is that failure to manage these amplifying factors results in treatment failure no matter how aggressively or appropriately the primary disease is treated. Our job is to identify and manage as many primary and secondary causes for itch, do our best to raise the threshold, modulate sensation, and eliminate factors that contribute to summation.

RECOGNIZING PRURITUS IN CATS

Some clinical signs of pruritus are obvious: for example, scratching the face, head, ears, and neck, with hind claws to the point of excoriation and self-mutilation (Table 1). Cats that "chew," "corn-cob," or "pull" hair with their teeth also are easily recognized. If pruritus is accompanied by visible evidence of inflammation or dermatitis, such as scale, crust, erythema, papules, plaques, or erosions, then clients and veterinarians are much more likely think pruritus. The difficulty arises when the only evidence is alopecia subsequent to excessive grooming, especially when the cats do not groom in front of owners. In many cases symmetrical alopecia of the flanks, ventral abdomen, limbs or tail, is the only sign of significant pruritus. Some cats have primary lesions, such as miliary dermatitis, eosinophilic ulcers/plaques/ granulomas of lips or haired skin, alopecia and scale on pinna, facial seborrhea, often associated with diseases that cause pruritus, but never appear to itch. The diagnostic approach to these cases is the same as the approach to pruritus, even if itch is not the most prominent clinical sign.

Differential Diagnoses

There are dozens of diseases that can cause cats to itch; however, 95% of cases will result from a smaller more manageable list caused by PAIN: Parasite, Allergy, Infection, Neoplasia.

- Parasite: Notoedres, Cheyletiella, Otodectes, Fleas, *Demodex gatoi*, Lice, Chiggers.
- Allergy: Atopy, Food, Contact, Mosquito bite hypersensitivity, Eosinophilic granuloma complex
- Infection: Bacteria, Malassezia, Dermatophyte, Herpes viral dermatitis
- Neoplasia: T-cell lymphoma

Less common primary causes of pruritus which should be included on a list of differentials for unusual cases or when the more common causes have been

Table 1. Clinical Manifestations of Pruritus

Primary Clinical Signs	Secondary Lesions	Associated Lesions
Scratching	Excoriation	Miliary dermatitis
Chewing	Scale	Ulceration
Corn-cobbing	Crust	Plaque
Licking	Erosion	Erythema
Excessive grooming	Hypotrichosis	Granuloma
Hyperesthesia	Symmetrical alopecia	Seborrhea

eliminated, include hyperthyroidism, drug eruption, vasculitis, erythema multiforme, urticaria pigmentosa, pemphigus foliaceus, and cholestasis.

Symmetrical Alopecia: Clinical Presentation, Diagnosis, and Management

A common presentation that is illustrative of my approach to feline pruritus is symmetrical alopecia due to excessive grooming. The cat tongue is a very efficient instrument to break off and remove hair shafts at the surface of the skin. The broken hair shaft remains in the hair follicle and are easily visible on physical examination. Examination of hair shafts under the microscopic demonstrates fractured ends, easily differentiated from the tapered end of a normal hair. Owners may or may not observe the patient grooming excessively. Swallowed hair may manifest as hairballs, frequent regurgitation, vomiting, or hair in stool. Scale or other evidence may be effectively removed by the patient. In most cases skin is quiescent, with no visible scale, crust, erythema, papules, pustules, or erosions.

This type of pruritus is frequently misdiagnosed as psychogenic alopecia based solely on clinical appearance. Excessive grooming is more commonly the result of pruritus than anxiety or obsessive-compulsive behavior disorders. In a recent study, evaluating 21 adult cats referred to a behavioral service with a presumptive diagnosis of psychogenic alopecia, a cause for pruritus was identified in 19 cats, with only 2 cats found to have only psychogenic cause. Adverse food reaction was the most common diagnosis, 12 cats confirmed by challenge feeding and 2 additional cats suspected but not confirmed. Other causes identified in this population included parasitism, flea allergy dermatitis, atopy, and hyperthyroidism. Psychogenic alopecia should only be diagnosed when all causes of pruritus have been eliminated from the list of differential diagnosis. The list of differential diagnoses can be intimidating and the ability to arrive at a definitive diagnosis can be difficult; however, achieving a final diagnosis and directing therapy at the cause of the itch is much more rewarding for patient, owner, and veterinarian than treating all causes of itch symptomatically with frequent steroid injections.

History

History is useful to rank differential diagnoses but rarely provides a diagnosis.

- **Determine the age of onset of clinical signs.** If less than 6 months, consider parasite hypersensitivity and dermatophytes the most likely cause of disease. Between 6 months and 6 years of age, any cause for pruritus is possible, with ectoparasitism, atopy, and food allergy the most likely differentials. In cats greater than 8 years of age, consider cutaneous T-cell lymphoma or hyperthyroidism.
- **Determine if the condition exhibits a high degree of seasonality.** If year round, you can not eliminate or even lower atopy on the list, since atopy may be non-seasonal; however, if there is a high degree of seasonality with extended periods of normalcy during predictable and repeatable cycles, then atopy is most likely, followed by seasonal insect triggers such as fleas and mosquitoes.
- **Determine if the condition was responsive to corticosteroid therapy.** As a general rule, atopy is highly responsive to steroids, parasite hypersensitivity is partially or temporarily responsive, and poor response to steroids is suggestive of food allergy.
- **Determine if lifestyle increases risk for contagious causes of pruritus,** such as Otodectes, Cheyletiella, fleas, or dermatophytes. Examples include a recently introduced animal, recent travel, or access to the outdoors.

Initial Diagnostic Approach

The initial approach should be aimed at finding parasites early, eliminating need to pursue other tests.

- Flea combing, ear swabs, acetate tape preparations, skin scraping and hair pluck in mineral oil to evaluate for Fleas, *Demodex gatoi*, *Otodectes*, and *Cheyletiella*. *D. gatoi* mites are the most elusive. Target hair pluck and deep and superficial scrapings on any area with inflammation or easily epilated hairs. If no areas exist, sample broadly across several regions; include areas the cat cannot reach easily, such as the back of the head and neck. Lower the condenser on the microscope to increase refraction and to avoid blasting light through the unstained mites.
- Performing skin scrapes on non-pruritic cats from the same household may yield positive results, since these cats don't care about their parasite burden and are not removing mites as efficiently.
- Fecal exams, because cats that are so efficiently grooming mites from skin may yield negative scrapes.
- If no mites or fleas, perform a Wood's lamp examination and collect dermatophyte culture.
- Begin to discuss food allergies and environmental allergies as the next focus once parasitism and dermatophytosis are definitively ruled out.

Parasite Treatment Trial

A parasite treatment trial is recommended for all pruritic cats. Remind owners that the absence of parasites on initial samples does not eliminate ectoparasites from the list of differential diagnoses. Selamectin applied topically every 2 weeks for three treatments is an effective protocol. Selamectin treats for fleas and Otodectes, and is anecdotally beneficial for Notoedres and Cheyletiella although not rigorously evaluated. Oral or injectable ivermectin provides no substantial advantages over selamectin and is not effective against fleas. Fipronil spray is effective against Cheyletiella, as well as fleas, but not Otodectes. Unfortunately no avermectin is consistently effective against *Demodex gatoi*. For *Demodex gatoi,* use Lime

Sulfur dip (8 oz/1 gallon) once weekly for 4 to 6 weeks. Although time consuming and malodorous, Lime Sulfur is safe, effective, mildly anti-pruritic, and has the added benefit of efficacy against dermatophytosis. A treatment trial with Lime Sulfur is the only method to rule out *Demodex gatoi*. In a multi-cat household, treat all animals to eliminate the possibility of repeat infestation during the treatment trial. If not possible to treat all in-contact animals, then the patient should be quarantined for the duration of the treatment protocol. If not parasite or dermatophyte, then consider food allergy, atopy, and hyperthyroidism.

Food Trials

A comprehensive elimination diet trial should be implemented as a diagnostic test. For a minimum of 8 to 12 weeks, the patient should be provided only an appropriate novel protein or hydrolyzed protein diagnostic test diet. The author prefers Rabbit/Green pea or any of the many hydrolyzed protein diets. Other pets may need to be isolated and dishes removed since even licking empty food dishes could provide enough of the offending protein to perpetuate pruritus and invalidate the diet trial. Stress to the owners that the diet food is not what makes their cat better; rather it is the absence of any offending proteins that is necessary for improvement. Furthermore, the diagnostic value of a diet trial is not how much better the cat gets while on the food, but whether or not clinical signs return when challenge fed with the original diet. Food trials can be performed concurrent with parasite treatment trials, since the diagnostic test is response to provocative challenge.

Allergen Testing

The purpose of specific allergen testing is to identify environmental allergens for inclusion in allergen immunotherapy injections, not to diagnosis atopy. Most cats will have several positive reactors by intradermal allergy testing or IgE allergy serology, but that does not mean those environmental allergens cause their disease. In cats with distinct seasonal pruritus or cats where other causes, such as parasites, dermatophytes, and food allergy have been eliminated, intradermal allergy testing or IgE allergy serology is appropriate. Selection depends on access to intradermal testing, ability to remove patient from medications that inhibit intradermal testings (antihistamines, corticosteroids), and safety of sedating patient. Serology is an acceptable substitute for intradermal allergy testing, if conditions for intradermal allergy testing cannot be met. Regardless of method, immunotherapy should be instituted with the understanding that this therapy is not immediately anti-pruritic. Rather, immunotherapy modulates immune response to allergens, decreasing severity of hypersensitivity reactions. This is a long-term therapy that diminishes clinical signs, but may not eliminate all manifestations of disease. The safety record for immunotherapy is excellent.

THERAPY

In addition to attempting to identify and manage the primary cause, therapy can be instituted to provide temporary relief of clinical signs; commonly referred to as symptomatic management. Basic therapies include cooling, topical sprays/lotions, omega III fatty acids, antihistamines, corticosteroids, and cyclosporine. Cooling methods commonly applied to dogs, such as frequent cool water baths, oscillating fans, menthol, or witch-hazel sprays, are less useful for cats since they may not be readily accepted by the patient. Topical sprays and lotions may also be resisted by some cats, but can provide benefit if the cat is not permitted to groom after application. Prolonged usage of potent topical steroids (betamethasone, dexamethasone, triamcinolone) can have severe adverse effects, including permanent skin thinning and hyperfragility. Topical steroids should only be used for short periods.

Oral omega III fatty acids and antihistamines may be beneficial in a mildly pruritus, but are less likely to provide satisfactory results in severely affected patients. Data on use in cats is woefully inadequate. Omega III fatty acids, should not be used during a food trial, since fish is a common dietary protein in cats. The dosage of EPA (eicosapentanoic acid) should be approximately 180–200 mg/day. Alone, fatty acids are not likely to substantially reduce pruritus; however in combination with other therapies fatty acids can be beneficial, even reducing the amount of corticosteroid required. Antihistamines are most useful for atopy, with minimal benefit if any in other pruritic diseases. Table 2 provides a list of antihistamines used in cats and suggested doses. Antihistamines are very safe, with minimal side effects or contraindications. Failure to respond to one antihistamine does not mean the patient wouldn't respond to a different antihistamine. Try several in two week trials before abandoning hope.

Table 2. Suggested Antihistamine Dosages for Cats

Chlorpheniramine maleate	0.25 mg/kg up to TID
Clemastine (Tavist®)	0.05 to 0.1 mg/kg BID
Cyproheptadine (Periactin®)	0.5 to 1.0 mg/kg up to TID
Hydroxyzine HCl (or pamoate) (Atarax®)	1.0 to 2.0 mg/kg up to TID
Amitriptyline	5 to 10 mg/cat SID or divided BID

Corticosteroids are the most effective method of providing immediate and substantial relief from symptoms. Therapy should be designed to provide temporary humane relief from refractory pruritus, but never as a substitute for appropriate diagnosis and management of primary disease and secondary infections. Long term glucocorticoids can have disastrous consequences, including increased risk for secondary infections, diabetes, and most horrifically feline cutaneous hyperfragility syndrome, characterized by thin fragile skin that tears very easily and very permanently.

When using glucocorticoids to manage pruritus, the least amount needed to provide relief, for the shortest period of time is the rule. Because cats are slow to convert prednisone to metabolically active forms, always use prednisolone or methylprednisone directly. If a cat fails to respond to appropriate prescribed dosage, verify that prednisone was not dispensed inadvertently. Oral triamcinolone and dexamethasone are acceptable for short-term usage in cats. Our knowledge of the metabolism of the various synthetic corticosteroids in veterinary patients is not adequate. Most information on absorption, half-life, and relative potency is extrapolated from human literature. A recent study comparing glucocorticoids at immune suppressive doses in cats, supported the hypothesis that dexamethasone had higher diabetogenic effects than prednisolone. This may be due to a variety of factors, but suggests that if long-term high-dose steroid is necessary for managing a feline patient, prednisolone is preferred over dexamethasone. In general, use oral steroids at high initially daily dosage to suppress pruritus, then diminish to the lowest alternate-day dose that maintains symptoms. Use of steroids in combination with oral antihistamines may extend the time between doses or lower the overall amount of steroid necessary to maintain satisfactory clinical response. Depo-Medrol (methylprednisolone acetate) is recommended primarily for management of eosinophilic granuloma complex or in atopic cats where other diagnostic and therapeutics have been exhausted.

Microemulsified cyclosporine provides an alternative to corticosteroids for cats that require long-term symptomatic management, or who fail to respond satisfactorily to management of the primary disease. Although anecdotally effective at 5 mg/kg daily for pruritus and eosinophilic granuloma complex, cyclosporine has not been rigorously evaluated in cats. In general, cyclosporine does not provide the rapid cessation of pruritus achieved with corticosteroids, but can be used for long term treatment with relatively fewer adverse consequences. Nausea, inappetence, and vomiting are the most common side effects. Fatal systemic toxoplasmosis has been reported. Avoid use in cats with high risk for toxoplasmosis, such as hunters. Toxoplasmosis titers can be performed prior to administration.

Allergen-specific immunotherapy (ASIT) provides a non-drug option for long-term treatment of atopy. While not directly antipruritic, ASIT modulates response to allergens and diminishes severity of hypersensitivity reactions. The precise mechanism of action is not known; however, the safety record is very good and there is excellent evidence for efficacy. Response rates as high as 70% have been reported for ASIT in feline patients. Cats may require adjunctive therapy, such as antihistamines or intermittent corticosteroids, for maximal benefit. Either intradermal allergy testing or serum IgE allergy serology is appropriate methods for determining which allergens should be included in therapy.

CANINE PRURITUS – PRACTICAL GUIDE TO MANAGEMENT

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WHAT IS PRURITUS?

Pruritus is medical term derived from the Latin *prurire*, meaning itch. Three hundred and forty years ago, Samuel Hafenreffer defined pruritus as "an unpleasant sensation provoking the desire to scratch." If you feel an itchy sensation, you scratch near it in order to change your perception of that sensation. Since our patients might also rub, lick, scoot, chew, roll, or shake, or press their backs up against the coffee table as well, we must expand the definition to include these other symptoms.

Threshold

Pruritic mediators or sensations are not equal in their ability to elicit itch. If sensation exceeds threshold you itch, otherwise you don't. The same stimulus may or may not induce pruritus depending on individual threshold and the circumstances that influence threshold at that moment.

Modulation

Psychological state can raise or lower threshold. Activity or other stimulation can distract a patient from scratching without changing the pruritic mediators or sensation. When left alone an atopic cat may lick rhythmically for hours, but when the family comes home, another pet is introduced, or food is present, they stop itching immediately. When the house becomes quiet and dark at night, the dog returns to licking or scratching. Some itch so intensely that no amount of stimulation or physical restraint distracts them. Sarcoptes and food allergy can stimulate self-mutilating pruritus. We can modulate psychological states to reduce pruritus by recommending environmental enrichment.

Summation

Multiple stimuli can add up to exceed threshold and worsen the severity of pruritus. For example, an atopic dog may not itch when exposed to ragweed pollen alone, but becomes pruritic when secondary factors such as dry skin, fleas, or bacterial infection are present. With secondary factors, patients may require high dose steroids to control pruritus. By preventing fleas and treating infection, pruritus is more easily managed with relatively safe drugs. A corollary is that failure to manage these amplifying factors results in treatment failure no matter how aggressively the primary disease is treated. Our job is to identify and manage as many causes for itch as possible, then do our best to raise the threshold, modulate sensation, and eliminate factors that contribute to summation.

TOP FIVE PRIMARY CAUSES OF PRURITUS IN DOGS

1. Atopy
2. Food allergy
3. Parasite hypersensitivity (fleas, Sarcoptes, Cheyletiella, or Otodectes)
4. Malassezia dermatitis
5. Staphylococcal pyoderma

To make it even easier, Malassezia dermatitis and Staphylococcal pyoderma are almost always complications of atopy, food allergy, or parasite hypersensitivity. You just need to do cytology to determine #4 and #5, treat, and then only worry about #1–3. Less common causes of pruritus include actinic dermatosis (sun damage), cutaneous larval migrans, contact reactions, adverse drug reactions, biting flies, dermatophytosis, T-cell lymphoma, vasculitis, and pemphigus, cholestasis

DIAGNOSIS

History

None of the top five causes for pruritus can be definitively ruled in or out by history, but they can be ordered differently based on history:

- **Age of onset?** If less than one year, think parasite hypersensitivity or Demodex. Between 1 and 4 years of age, anything is possible, but atopy is number one. Over 6 years of age, food allergy becomes more likely than atopy, but also start thinking hard about endocrinopathies.
- **Seasonality?** Definite seasonality is usually atopy or flea allergy dermatitis. Year-round pruritus doesn't eliminate atopy or flea allergy, but you get to pile on other differentials.
- **Higher risk for parasite exposure?** Recent adoptee in household? People or other animals in household itching?
- **Regular flea/tick control?**
- **Previous treatment?** Antibiotics/steroids/thyroid supplementation? Response? If highly steroid-responsive bump up atopy. If not steroid-responsive, bump down atopy and bump up food allergy, endocrinopathies, and unusual dermatoses such as T-cell lymphoma or erythema multiforme.

Breed

Not particularly useful, but can lead you astray, convincing you that a fox terrier has to be atopic when it really just has Sarcoptes (don't worry it will develop atopy later). Breed predisposition lists are over long, change based on breed popularity, change geographically, and change over time often enough to be rendered nearly meaningless. Any dog can be atopic, food allergic, acquire parasites, or become overpopulated with native Malassezia and/or Staphylococcus. Ignore breed and approach all itchy dogs the same.

Physical Examination

Atopy and food allergy look identical in the exam room, but two areas to look for atopy are the anterior flexural surface of elbow and the posterior carpus between pad and accessory carpal pad. Flea allergy tends to affect the back half of the dog worse, with classic signs of alopecia, erythema, papular dermatitis at dorsal tail head. Sarcoptes is most commonly associated with the pinna, elbows, flank; but not always. Never rule out Sarcoptes based on physical examination alone. Any dog that itches can be a Sarcoptes dog. Cheyletiella is usually indicated by dry scale on the dorsum. Check for a pinnal-pedal reflex by rapidly scratching the leading edge of the pinna with a finger nail. If the ipsilateral leg starts stratching, then the test is positive. This test is positive in majority of Sarcoptes dogs, but negative with most other pruritic diseases, and is a rough tool, but if positive a parasite treatment trial is always indicated. Don't rule out Sarcoptes based on negative pinnal-pedal reflex. Check for concurrent otitis. As a general rule, if no infection to affect signs, atopy affects the pinna and opening most, while food allergy generally affects the horizontal and vertical canal more. If infection is present, this is no help. Crusting on edge of pinna is strongly suggestive of Sarcoptes.

Diagnostic Testing

Every patient gets cytology, skin scraping, and a parasite treatment trial.

- Perform cytology for bacteria and yeast. Major cause of pruritus complicates diagnosis of allergic disease. May be primary cause of pruritus in patients with hypothyroidism, etc.
- Skin scrape for Sarcoptes, Cheyletiella, Demodex. Negative scraping does not rule out either; however, if you get lucky and find mites, then no need to keep going with other diagnostic testing
- Parasite treatment trial is an essential part of a logical diagnostic plan for pruritus. The author prefers selamectin: every 2 weeks for three treatments. Alternatives include milbemycin at 2 mg/kg once weekly for 4 weeks or ivermectin 300 µg/kg once weekly for 4 weeks. Since any breed can be ivermectin sensitive, always titrate up to the full dose. Fipronil spray is useful for Cheyletiella, but is ***not*** effective at eliminating Sarcoptes, and therefore not useful for treatment trials. Lime sulfur dip is an excellent and safe miticide, that also happens to help with dermatophytosis, but is kind of smelly!
- Eight-week elimination diet trial followed by challenge feeding is the next step. Ideally a home-cooked diet of 50:50 pinto beans/yams, or you can add exotic meats such as kangaroo, ostrich, alligator, frog legs (check out www.exoticmeats.com). Rabbit/potato is my favorite novel protein diets. Recent study showed poor results with venison- or fish-based test diets; may be fine maintenance diets. Hydrolyzed protein diets are also a good choice, but not 100% either. Regardless of diet choice, the response to provocative challenge is the diagnostic part of the test!
- Food serology is awful at identifying the specific protein to which a patient is allergic; however, if positive for more than five ingredients, then food allergy is likely (and not just to those five ingredients)
- Antigen-specific intradermal testing or serology is not diagnostic to prove a patient has atopy, but is used to determine what allergens to put into immunotherapy
- Antibiotic or antifungal treatment trial. If unsure if infections are the reason for itch, or a consequence of a primary pruritic disease, then treat then re-evaluate. The author recommends cefpodoxime 5–10 mg/kg once daily or cephalexin 20 mg/kg BID for 30 days and ketoconazole 5 mg/kg once daily for 30 days. Combine with weekly antiseptic shampoo: Chlorhexidine, ketoconazole, miconazole, benzoyl peroxide. Focus on problem areas first; leave on 10 minutes
- Dermatophyte culture. Not a top five cause, but a good rule out if patient does not have one of the top five
- Biopsy is THE ESSENTIAL diagnostic test for any pruritic patient you can't place in the top five

THERAPY

In addition to identifying and managing primary causes, therapy should be instituted to provide temporary relief of clinical signs. Basic therapies include cooling, topical sprays/lotions, omega III fatty acids, antihistamines, corticosteroids, and cyclosporine. Cooling methods can modulate threshold and decrease pruritus. Try frequent cool water baths, an oscillating fan, menthol, or witch-hazel spray.

Omega III fatty acids and **antihistamines** may be beneficial in a mild pruritus, but are less likely to provide satisfactory results in severely affected patients. The dosage of EPA (eicosapentanoic acid) should be approximately 40 mg/kg/day. Alone fatty acids are not likely to substantially reduce pruritus; however, in combination with other therapies fatty acids can be beneficial, even reducing the amount of corticosteroid required. Do not use omega III fatty acids during food trials. Antihistamines are most useful for atopy, with minimal benefit if any in other pruritic diseases. Antihistamines are very safe, with minimal side-effects or contraindications. Failure to respond does not mean the patient wouldn't respond to a different antihistamine. Try several for a 2-week trial before abandoning hope.

Glucocorticoids

Glucocorticoids are the most effective method of providing immediate, substantial relief from pruritus. Evidence supports good to excellent response in 75% to 97% of atopic patients, using various study designs, drugs, and dosages. The goal of steroid therapy is temporary humane relief from refractory pruritus, but should never be a substitute for diagnosis and management of primary disease and secondary infections. Nor should steroids be first choice therapy for mildly affected patients. Overall steroids are safe and effective for short courses; however, even at low doses long-term glucocorticoids can have disastrous consequences. A recent prospective study (Torres SM JAVMA 2005; 227(2):239-243) showed that 23 of 127 dogs (18%) receiving long-term glucocorticoids for pruritic disorders had bacteriuria (vs. 0 of 94 dogs not on steroids). Bacteriuria may be "silent" as inflammation is suppressed and urine is dilute. Do not rely on sediment to screen for urinary tract infection (UTI). Recommend urine culture quarterly on all patients on prolonged course of glucocorticoids.

Our knowledge of the metabolism of the various synthetic corticosteroids in veterinary patients is not adequate. Most information on absorption, half-life, and relative potency is extrapolated from human literature. However, experience tells us that oral prednisone is a good first choice for dogs, especially when used in combination with antihistamine to reduce total steroid dose. Prescribe a high dose initially to break the itch-scratch cycle, then rapidly reduce to lowest alternate-day dosage that maintains relief. A common protocol is 0.5 mg/kg BID for 2 to 3 days, then once daily for 2 to 3 days, then twice daily. In general I prefer alternate-day dosing over once daily dosing, even if a higher dose must be given. For example, I'd rather give 20 mg every other day than 10 mg SID. How much is too much? Aim for a total dose in 12 months below the dog's weight (lbs) x 15. For example, an 80 lb Labrador should not exceed 1200 mg/year or sixty 20-mg tablets, or 600 Temaril-P (2 mg pred each). Methylprednisolone (Medrol) is slightly more potent than prednisolone. Multiply prednisone dose by 0.8 to get the methylprednisolone dosage (ie, 4 mg methylprednisolone = 5 mg prednisolone). Methylprednisolone is reported to have less polyuria/polydipsia (PU/PD) associated than prednisone or prednisolone. Dexamethasone and triamcinolone are good second choices due to longer half life and more pronounced long-term side-effects, such as thin skin and weak tendons. Recent evidence points to dexamethasone having a higher diabetogenic potential than prednisone. If a patient develop poor response to prednisone and if no other cause can be identified (pyoderma, Malassezia), try steroids from a different class. You may be able to return to prednisolone later.

Oral forms have rapid absorption and high bioavailability, so injectable steroids provide minimal benefit over oral forms unless owners cannot give pills (primarily an issue for cat owners). Injectable dexamethasone or prednisolone sodium succinate can be useful in emergency hypersensitivity situations, such as anaphylaxis or severe self-traumatizing pruritus. Depo-Medrol (methylprednisolone acetate) is used primarily in cats for management of eosinophilic granuloma complex or in atopic cats where other diagnostic and therapeutics have been exhausted. Significant disadvantages include not being able to tailor dose to patients needs or provide days off steroids. Depo-Medrol has no great value in managing dogs, other than convenience to owners at the expense of the dog's well-being.

Topical steroids, such as Genesis spray (0.015% aqueous triamcinolone), are useful for short-term relief of pruritic dermatitis when systemic steroids may not be indicated. Topicla steroids can alter adrenocortical access and will cause cutaneous thinning and milia if overused by clients. Recommend strict adherence to label recommendations. Steroid ointments have limited benefit except in the most focal pruritus

Microemulsified Cyclosporine (CsA) has multiple mechanisms of action: it inhibits T-cell activation, mast cell survival, response, histamine release, prostaglandin production, cytokine production, eosinophil migration, survival, and degranulation. Independent research demonstrates that CsA works! It really, really does! In a 13-dog comparison with prednisone therapy, CsA had equal efficacy: 10/13 (77%) responded with >50% reduction in pruritus and skin lesion scores. In a larger, 51-dog study, good to excellent response was reported in 78% of patients; 28/51 dogs continued therapy, with 10 on daily dose and 18 every other day or less. For dogs that discontinued therapy 12 of 51 (24%) stopped after achieving remission and did not relapse for an average of 12 months! Eleven of 51 (22%) stopped therapy prior to response because six owners felt there was no apparent benefit and five owners stopped for cost. Overall client satisfaction was great; 71% would use again, 17% maybe, and only 12% said no. No adverse events were reported in 78%.

Contraindications include neoplasia, demodicosis, dermatophytosis, and systemic fungal infection. Use with caution in hypertensive patients. The most common adverse reactions are vomiting, diarrhea, anorexia, and weight loss. Bacteriuria was reported in 8% of patients in one study (versus 18% with low-dose steroid). Less than 2% of patients experience cutaneous papillomatosis, gingival hyperplasia, hirsutism, periodontitis, cutaneous lymphomatosis (plaque) lesions that look like T-cell lymphoma, but go away when therapy is discontinued). At 5 mg/kg, side effects that are NOT SEEN include hepatotoxicity, nephrotoxicity, or myelotoxicity.

Cyclosporine does not replace diagnosis of primary cause for itch. Rule out parasites, infection, and food allergy prior to starting therapy. CsA is a really cool drug, but it doesn't kill fleas or Sarcoptes! For severely pruritic patients consider administering it along with prednisone. Since there is a lag period before CsA suppresses pruritus, prednisone can provide excellent relief while waiting. Aim for 5 mg/kg one time daily, but remember to decrease dose in obese patients because CsA is highly lipophilic. A human study showed increased serum levels correlated with increased obesity index. Ideally give on an empty stomach if at all possible (2 hours before meals), since giving with food decreases absorption. To mediate GI symptoms some dermatologists give with a meal for the first 10 to 14 days, and then switch to empty stomach plan. The vomiting appears to be dose dependent and temporary if you can get through the initial weeks. It can be combined with ketoconazole to decrease dose (and therefore cost). Ketoconazole competes with p450 metabolism of CsA resulting in higher serum levels. Ketoconazole given at a dose of 5–10 mg/kg reduces CsA dose by 50%

Recheck in 4 to 6 weeks. If the patient is doing brilliantly, then slowly decrease to every other day dosing. Drop one day per week with every new box of 15 capsules. For example, drop Tuesday. Next box, drop Tuesday and Thursday. Next box, drop Tuesday, Thursday, and Saturday. Next box, drop Tuesday, Thursday, Saturday, and Sunday (giving only Monday, Wednesday, and Friday). If the patient continues to do well, decrease to twice weekly or even once weekly. If pruritus returns at lower dose, go back to the last effective dose and try to decrease again in 3 months. If not achieving expected results, continue once daily dosing until maximal benefit then decrease to every other day. Seventy-five percent of patients that are clinically improved at 4 weeks will be able to decrease to every other day. Check for gingival hyperplasia (about 1 in 200 cases) and for profound proliferative change. Check for warts. For the one in four dogs that manifest GI disturbances you can stop for 3 to 4 days, restart with meals, restart at lower dosage, restart with dose divided BID, or give with metoclopramide, which is effective at suppressing vomiting but may affect hepatic metabolism resulting in higher than expected serum levels.

Allergen-Specific Immunotherapy

Allergen-specific immunotherapy (ASIT) provides a non-drug option for long-term treatment of atopy. While not directly antipruritic, ASIT modulates response to allergens and diminishes severity of hypersensitivity reactions. The precise mechanism of action is not known; however, the safety record is very good and there is excellent evidence for efficacy. Response rates as high as 70% have been reported for ASIT in veterinary patients. The earlier you start, the better. In human children, ASIT has been shown to alter or even stop progression of disease when used early. Evidence in dogs demonstrates best response when started earlier than fifth year of clinical signs. ASIT has a great safety record in dogs with only one reported case of anaphylaxis in a dog. In humans, severe life-threatening reactions can occur, but are almost always in asthmatics, not patients with atopic dermatitis. Facial edema, urticaria, lethargy, and anxious behaviors are reported in dogs but are uncommon. Increased pruritus and local injection site reactions are more common (up to 25% of cases).

METHICILLIN-RESISTANT STAPHYLOCOCCUS AND YOU

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Methicillin-resistant *Staphylococcus aureus* (MRSA) has already arrived as a major crisis in human healthcare. Both hospital-acquired and community-acquired strains are running rampant in various geographic regions, creating significant morbidity in at risk populations and major headaches for hospitals and the Centers for Disease Control (CDC). MRSA accounts for 30% to 40% of all hospital-acquired infections in humans, making MRSA the most prevalent nosocomial infection worldwide. In the US, 1.3% of the general population carries MRSA. More recently, methicillin-resistant Staphylococcal species (MRSS), including resistant *S. intermedius, S. schleferi, and S. hyicus,* have emerged as a growing concern in veterinary medicine. A recent survey at the 2005 ACVIM Forum in Baltimore demonstrated that 27 of 417 veterinarians (6.5%) carried MRSA in their nasal passages. Large animal practitioners were at highest risk (15.6% positive) compared with small animal practitioners (4.4% positive). Infections by MRSS have been reported in horses, dogs, cats, cattle, sheep, rabbits, chickens, and parrots. MRSS outbreaks in equine hospitals are of grave concern both for morbidity/mortality of patients as well as documented zoonotic spread to veterinarians and staff. Small animal cases are generally associated with "reverse zoonoses" or acquisition from an owner with a link to a hospital environment. However, recent reports for animal-to-animal and animal-to-human transmission with no links to hospitals have raised concerns of more widespread risk to human health from animal reservoirs.

WHAT IS METHICILLIN RESISTANCE?

First, we created penicillin to treat bacterial infections. Penicillin and other beta-lactam ring antibiotics work by inactivating penicillin binding proteins (PBPs), which are essential for building of the bacterial cell wall. All four native PBPs in Staphylococcus are inactivated by beta lactams, resulting in osmotic lysis of bacteria. Sneaky bacteria developed beta-lactamases that cleave the antibiotic ring conferring resistance to those bacteria that produce enough of these enzymes to prevent the penicillin from inactivating their PBPs. Clever humans then developed semi-synthetic penicillins to overcome beta-lactamase producing bacteria. Examples of early semi-synthetics include methicillin, oxacillin, and cloxacillin. Sneaky bacteria develop methicillin resistance almost immediately! Methicillin was introduced in 1959 and MRSA was first reported in 1961. Methicillin resistance results from the gene mecA, which codes for production of PBP2a, a non-native PBP that has very low affinity for beta-lactam antibiotics. If you produce PBP2a you have complete resistance to all beta-lactam antibiotics.

Short answer: MecA gene = methicillin resistant PBP = resistance to all beta-lactam antibiotics.

WHY SHOULD I CARE ABOUT MRSS?

MRSA adds a level of treatment challenge to any individual MRSS-positive veterinary patient. Traditional antibiotics don't work for MRSS pyodermas, urinary tract infections (UTIs), ear infections, pneumonia, or osteomyelitis. Moreover, there is a significant zoonotic concern for transmission from infected patients to the owner and veterinary healthcare providers. Veterinarians and staff may then become carriers and transmit to other patients. Additionally, creation of an animal reservoir for transmission to humans is of grave concern. Veterinarians risk CDC regulation of antibiotic usage if zoonotic MRSA is perceived to be a major threat to human population.

WHEN TO SUSPECT MRSS IN YOUR PATIENT?

The tricky thing about recognizing MRSS is that most strains are no more virulent or toxic than *S. intermedius*, just more resistant to treatment. Thus, clinical signs of MRSA are identical to regular old *S. intermedius* infections. MRSS is associated with pustular or follicular pyoderma, abscess, postoperative wound infection, or nosocomial IV catheter site infection. Orthopedic surgical implants are a common site for MRSA. Less commonly veterinary patients present with pneumonia, rhinitis, bacteremia/sepsis, septic arthritis, osteomyelitis, pyometra, or mastitis. Basically any suppurative infection can be MRSS.

Become suspicious if a suppurative infection with gram positive cocci responds poorly to empirically effective antibiotics (cephalosporins, Clavamox, fluoroquinolones). Be particularly suspicious if a person in the household has MRSA or a link to human healthcare.

HOW TO IDENTIFY MRSS?

First, perform cytology to confirm the presence of coccoid bacteria (Diff-Quik is fine). Submit culture swab. Be aware that most labs will call any coagulase-positive *Staphylococcus* isolated from a dog *S. intermedius*, even if it really is a different species of Staphylococcus. Most commercial labs do not perform tests necessary to differentiate *intermedius* from *aureus* or *schleferi*. This is should not be acceptable.

How do we know if our isolate is methicillin-resistant? Since methicillin is no longer commercially available in the US, it does not appear on the antibiotic susceptibility panel. Oxacillin is the standin for methicillin. The true test is if the animal carries the MecA gene or expresses PBP2a, but in general if an organism is reported as oxacillin-resistant, assume methicillin resistance. If oxacillin shows up as resistance, the lab is supposed to automatically report all beta-lactam agents as resistant even if in vitro testing shows susceptible. This means an "R" is populated next to all penicillins, synthetic penicillins, clavulanic acid-augmented penicillins, cephalosporins, carbapenems, and cephems. Unfortunately, some labs are slow to catch on to the presence of MRSA in veterinary patients, and still report "S" if in vitro susceptibility criteria are met. Personally I think it should be a criminal offense for veterinary laboratories to report susceptibility to these antibiotics in an oxacillin-resistant strain. **Bottom-line:** Do not use any beta-lactams for an oxacillin-resistant strain regardless of the lab report.

In addition to inconsistencies in laboratory reporting of MRSA, there are other disadvantages of using the antibiotic susceptibility profile for identification of MRSA. On the swab you submit, there may be mixed subpopulations co-existing that all look the same on the initial culture plate. Since the technician only selects one colony for susceptibility testing there is a definite opportunity for failure to identify the MRSA colony. Conversely, false positives do occur. A strain may be resistant to oxacillin in vitro but not be a carrier of the mecA gene, leading to inappropriate concern and management.

Additional testing can be performed to verify MRSA. Polymerase chain reaction (PCR) detection of mecA is the gold standard for identification and is available at some university microbiology laboratories. Additionally, Latex agglutination test can be performed to detect PBP2a. The CDC laboratory can analyze strains of MRSA to differentiate sub-types of MRSA (ie, hospital acquired versus community acquired). This is only desirable if there is a human in contact with the veterinary patient that has been infected by MRSA.

HOW TO TREAT MRSS?

Antibiotic treatment should be based on susceptibility testing and extended for 2 weeks beyond complete resolution. For surgical implant-associated infections, remove implants. Very few antibiotics are effective against the "hospital acquired strains." Basically, they are resistant to all beta-lactams, tetracycline, aminoglycosides, macrolides, chloramphenicol, and fluoroquinolones. Since 1996, vancomycin-resistant strains have been identified in humans—YIKES! "Community acquired strains" tend to be less scary on panels, but much scarier in concept since they could be lurking anywhere people gather. Typically the community acquired strains are resistant to only beta-lactams and erythromycin. Human cases are usually treated with vancomycin, linezolid, or daptomycin, or if susceptible, with trimethroprim/sulfa, gentamicin, or rifampicin.

For veterinary cases, regardless of what the lab report says, consider all strains resistant to penicillins, cephalosporins, cephems, ampicillin-sulbactam, amoxicillin-clavulanic acid, ticarcillin-clavulanic acid, piperacillin-tazobactam, and carbapenems. Veterinary isolates have variable resistance to gentamicin, rifampicin, cirprofloxacin (and other fluroquinolones), fusidic acid, co-trimaxazole, and tetracycline. More commonly they are susceptibility to amikacin, vancomycin, chloramphenicol, trimethroprim/sulfa, clindamycin, linezolid, and daptomycin. Generally avoid all beta-lactams and fluoroquinolones. Base treatment on susceptibility – trimethoprim/sulfa, chloramphenicol (55 mg/kg TID), clindamycin and aminoglycosides. Topical mupirocin ointment can be effective for some skin infections. Benzoyl peroxide wipes (Stridex Power Pads) can be useful for chin acne MRSA.

PREVENTION

Good hygiene is the single most important factor for prevention. Hand washing before and after every patient...and don't touch your nose. In a study at John Hopkins, doctors were much worse than nurses at washing their hands between patients (as few as 18%—YIKES). Extensive retraining, education, threats, rewards, and eventually circulation of photos of culture plates taken from hand prints at the staff cafeteria, resulted in compliance exceeding 90%. Environmental disinfection techniques should be regularly reviewed and reinforced in all clinical situations. *S. aureus* can remain viable for 17 hours in direct sunlight, 46 hours on clean glass surfaces, and up to 7 days on floors. I don't know about keyboards, telephones, and pens stuck in mouths, but probably longer than the period between the last time your colleague used it and you touched it....and then your nose. Men's ties were found to be excellent place to find MRSA in the human hospital setting. Trust no one.

Equine practices should establish screening and surveillance programs of patients and staff. Pets used in hospital and nursing home environments should be screened for nasal carriage. In humans, intranasal mupirocin is used to eliminate nasal carriage. This is impractical in dogs and cats. One asymptomatic carrier dog had MRSA successfully eliminated with oral doxycycline and rifampin. No acceptable options have been developed for horses.

SCARY STUDIES ABOUT METHICILLIN-RESISTANT STRAINS IN ANIMALS

- In horses, colonization by MRSS ranged from 2 to 130 cases per 1000 horses sampled across various farms, hospitals, and geographic regions. Foals in neonatal intensive care units are at high risk.
- In a survey of 7 North American veterinary teaching hospitals, 6 reported isolation of MRSA
    - 14% of all *S. aureus* isolates from animals were methicillin resistant
- A similar study in the UK found MRSA in 1.4% of all bacterial cultures.
- Documented zoonotic and reverse zoonotic cases:
    - Nurse involved in MRSA outbreak in nursing home was asymptomatic carrier, wasn't successfully treated until the same isolate was found and treated in her pet dog
    - Nasal cavity carriage of asymptomatic dog was implicated in recurrent MRSA infection in diabetic patient
    - Similar situation of woman with throat carriage of MRSA strain found in her dog
    - During an outbreak of MRSA in a geriatric nursing home, the resident cat became a carrier and the outbreak did not resolve until the cat was removed from the ward

  - In a veterinary clinic, five cases of postoperative MRSA infections were traced to the veterinarian as carrier of the same strain. Retrospective analysis estimated that strain was present in clinic for 2 years before detection
  - During outbreak of MRSA in a Veterinary Teaching Hospital Equine facility, 26 staff members were asymptomatically colonized. One veterinarian had a tattoo infection. Three personnel developed MRSA pyoderma after contact with a single sick foal
  - In a survey of a Veterinary Hospital in UK, MRSA was isolated from 14 of 78 staff members (18%), 4 of 45 dogs, and 3 of 30 environmental sites. Fluoroquinolone resistance was found in all isolates
- Retrospective survey of all staphylococcal isolates at the University of Pennsylvania (2003–2004)
  - 569 dogs/cats/birds/rabbits with positive culture for *Staphyloccoccus* sp.
    - 336 *S. intermedius*, 122 *S. schleiferi*, and 111 *S. aureus*
  - 145 of 569 had a methicillin-resistant strain (25.5%)!!!!!
    - 17% of *S. intermedius*, 40% of *S. Schleiferi*, 35% of *S. aureus* had methicillin resistance
  - 130 MR isolates were from dogs (0.6% of hospital population)
  - The oral antibiotic with the most reliable effect was chloramphenicol (95% sensitive), followed by trimethoprim-sulfa (68%)
  - Broad fluoroquinolone resistance was seen in the methicillin-resistant strains
    - 45% resistance in *S. intermedius*, 65% in *S. Schleferi*, 90% in *S. aureus*
  - Prior exposure to fluoroquinolone antibiotics is a risk factor for methicillin-resistant strains
  - Conclusions: Prevalence of *S. aureus* and *S. schleferi* is higher than previously thought. Prevalence of methicillin resistance is much higher than expected at VHUP. Fluoroquinolones are not a good choice for methicillin-resistant strains

Author Dan Morris states, "The ever increasing prevalence of 'human' strains in animal reservoirs suggests that perhaps it may be time for a paradigm shift in veterinary medicine...Veterinarians should no longer accept the one pathogen–one host concept."

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TOP FIVE REASONS DOGS ITCH!

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Pruritus is defined as an unpleasant sensation that provokes the desire to scratch….or in our patients… rub, lick, scoot, chew, roll, shake or press against the coffee table. Pruritus is one of the most common reasons owners present their dog to the veterinarian. Short-term symptomatic management of most pruritus can be achieved with corticosteroids, but unfortunately corticosteroids don't usually resolve the cause of the itch, mask signs of ongoing or worsening disease, and are not generally suitable for long-term management of most conditions. As a result, the patient feels better, the course of therapy ends, and the itch returns, in some cases worse than before. Chronic recurring pruritus becomes a major source of frustration and misery for patient, owner, and veterinarian.

Ideally, for long-term management veterinarians should pursue the cause of the pruritus while providing short-term symptom relief. In order to pursue the cause, we need to have a good list of differential diagnoses. As an exercise I had my resident list as many distinct conditions which have pruritus as a clinical sign as she could; she came up with 43 diseases. The problem is that for a lot of these conditions there is no single pathognomonic clinical sign to differentiate this cause for pruritus from the other—basically there are lots of diseases that make dogs itch and they all look pretty much the same.

So armed with the knowledge that there are lots and lots of differential diagnoses for pruritus, how should one proceed? First, don't try to rule out 43 differentials the first visit. Second, realize that 95% to 98% of patients presenting for pruritus will have one of the top five causes, so you can ignore the other 38 differentials in the vast majority.

THE TOP FIVE

1. Atopy
2. Food allergy
3. Parasite hypersensitivity (Fleas, Sarcoptes, Cheyletiella, or Otodectes)
4. Malassezia dermatitis
5. Staphylococcal pyoderma

That's it! To make it even easier, Malassezia dermatitis and staphylococcal pyoderma are almost always complications of atopy, food allergy, or parasite hypersensitivity. So, pretty much you just need to do cytology to determine #4 and #5, treat them directly, and only worry about #1, #2, and #3.

DIAGNOSIS

History

None of the top five causes for pruritus can be definitively ruled in or out by history, but they can be ordered differently based on history

- **Age of onset?** If less than one year, think parasite hypersensitivity or Demodex. Between 1 and 4 years of age, anything is possible, but atopy is number one. Over 6 years of age, food allergy becomes more likely than atopy, but also start thinking hard about endocrinopathies.
- **Seasonality?** Definite seasonality is usually atopy or flea allergy dermatitis. Year-round pruritus doesn't eliminate atopy or flea allergy, but you get to pile on other differentials.
- **Higher risk for parasite exposure?** Recent adoptee in household? People or other animals in household itching?
- **Regular flea/tick control?**
- **Previous treatment?** Antibiotics/steroids/thyroid supplementation? Response? If highly steroid-responsive bump up atopy. If not steroid-responsive, bump down atopy and bump up food allergy, endocrinopathies, and unusual dermatoses such as T-cell lymphoma or erythema multiforme.

Breed

Not particularly useful, but can lead you astray, convincing you that a fox terrier has to be atopic when it really just has Sarcoptes (don't worry it will develop atopy later). Breed predisposition lists are over long, change based on breed popularity, change geographically, and change over time often enough to be rendered nearly meaningless. Any dog can be atopic, food allergic, acquire parasites, or become overpopulated with native Malassezia and/or Staphylococcus. Ignore breed and approach all itchy dogs the same.

Physical Examination

- **Characteristic lesions:** Atopy and food allergy look identical in the exam room, but two areas to look for atopy are the anterior flexural surface of elbow and the posterior carpus between pad and accessory carpal pad. Flea allergy tends to affect the back half of the dog worse, with classic signs of alopecia, erythema, papular dermatitis at dorsal tail head. Sarcoptes is most commonly associated with the pinna, elbows, flank; but not always. Never rule out Sarcoptes based on physical exam findings. Any dog that itches can be a Sarcoptes dog. Cheyletiella tends to have lots of dry scale on the dorsum.
- **Pinnal-pedal reflex:** Rapidly scratch the leading edge of the pinna with a finger nail. If the ipsilateral leg starts stratching, then positive. This reflex is positive in majority of sarcoptes dogs, but negative with most other pruritic diseases. A rough tool, but if positive a parasite treatment trial is always indicated. Don't rule out Sarcoptes based on negative pinnal-pedal reflex.
- **Concurrent otitis?** As a general rule, if no infection to affect signs, atopy affects the pinna and opening most, while food allergy generally affects the horizontal and vertical canal more. If infection present, this is of no help. Crusting on the edge of

pinna without canal involvement is strongly suggestive of Sarcoptes.

Diagnostic Testing

Every patient gets cytology, skin scraping, and a parasite treatment trial. Really, every patient!

- **Cytology**
    - Bacteria and Yeast. Major cause of pruritus complicates diagnosis of allergic disease. May be primary cause of pruritus in patients with hypothyroidism, etc.
    - Occasionally see dermatophyte endospores
- **Skin scrape**
    - Superficial – Sarcoptes and Cheyletiella. Negative skin scraping does not rule out either parasite; however, if you get lucky and find Sarcoptes then no need to keep going with other diagnostic testing until these mites are eliminated
    - Deep – Demodex
- **Parasite treatment trial**
    - Essential part of logical diagnostic plan for pruritus
    - Selamectin: every 2 weeks for 3 treatments
    - Milbemycin: 2 mg/kg once weekly for 4 weeks
    - Ivermectin 300 µg/kg once weekly for 4 weeks. Caution: Step up to full dose
    - Frontline (fipronil) is not effective at eliminating Sarcoptes
- **8-week elimination diet trial followed by challenge feeding**
    - Home-cooked: 50:50 pinto beans/yams. Can add exotic meat, such as kangaroo, ostrich, alligator, frog legs (www.exoticmeats.com)
    - Rabbit/potato is my favorite novel protein diets. Recent study showed poor results with venison or fish-based test diets; may be fine maintenance diets.
    - Hydrolyzed protein diets. Good choice, but not 100% either
    - Amino acid formulation currently being evaluated—may be the answer.
    - Provocative challenge is the diagnostic part of the test!
    - Food serology is lousy at identifying specific protein to which patient is allergic; however, if positive to more than five ingredients, then food allergy is more likely.
- **Antigen-specific intradermal testing or serology** are not diagnostic tests to prove a patient has atopy, but are used to determine what allergens to put into immunotherapy.
- **Antibiotic or Antifungal treatment trial** – Treat secondary infections then re-evaluate.
    - Cefpodoxime 5–10 mg/kg once daily or cephalexin 20 mg/kg BID for 30 days
    - Ketoconazole 5 mg/kg once daily for 30 days
    - Weekly antiseptic shampoo: chlorhexidine, ketoconazole, miconazole, benzoyl peroxide. Focus on problem areas first, leave on 10 minutes. Use conditioners, too
- **Dermatophyte culture** – Hey, not a top five, but a good rule out if patient is not one of the top five
- **Biopsy** – THE ESSENTIAL diagnostic test for any pruritic patient you can't place in the top five

Never underestimate the power of bacteria or yeast to produce an inhumane level of itch. Always treat secondary infections aggressively and you might find those intractable atopics are much, much easier to manage. Treat the occult *Sarcoptes* and you will have even better results.

SKIN DISEASES THAT MIMIC PYODERMA – A CASE-BASED DISCUSSION

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Pyoderma can be defined as a pyogenic, or pus-producing, bacterial infection of the skin. Pyoderma has a widely variable presentation, with clinical signs that include papules, pustules, epidermal collarettes, erythematous macules, purulent exudation, folliculitis, furunculosis, and cellulitis.

Pyoderma in its many forms is an exceedingly common dermatosis in dogs. Forty to 60% of patients seen at dermatology referral centers have bacterial dermatitis as a component of their disease process. Many cases referred to dermatologists have failed to respond to treatment for superficial pyoderma. There are many reasons for treatment failure: (1) owner compliance, (2) wrong antibiotic, (3) inadequate dose, interval, or duration of prescription, (4) antibiotic resistance, (5) failure to identify underlying primary disease, or (6) not really pyoderma.

This case-based discussion focuses on reason number 6: not really pyoderma. By the end of the article you should be able to answer these questions:

1) What are the top three differential diagnoses for papules centered of follicles (ie, folliculitis)?

a. ____________________

b. ____________________

c. ____________________

2) Top three differential diagnoses for pustules?

a. ____________________

b. ____________________

c. ____________________

3) Three more differentials when the top three strike out? You can come up with more than three!!!

a. ____________________

b. ____________________

c. ____________________

4) What four diagnostic tests should be performed on every suspected pyoderma case?

a. ____________________

b. ____________________

c. ____________________

d. ____________________

5) What one diagnostic test should be performed when pyoderma doesn't respond to therapy?

a. ____________________

CASES

Case #1: Sampson

9-month-old, male neutered, Bernese Mountain Dog
History of recurring "hot spots" on face. Problem started after he was neutered 6 weeks ago.
Physical exam findings: Large patch of alopecia with purulent exudate. Many "satellite" papules centered on hair follicles.

Notes:

Case #2: Texas

4-year-old, male intact, American Game Dog
History of progressive alopecia with crusts, erythema, and exudation. Not responsive to cephalexin
Physical exam finding: Generalized disease affecting all areas of haired skin

Notes:

Case #3: Lady

6-year-old, female spayed, Chinese Pug
History of atopy with seasonally recurrent inguinal pyoderma. This year getting worse instead of better with same treatment protocol.
Physical exam findings: Intense focal pruritus on ventral abdomen/inguinal region. Large pustules, erythematous macules, comedones

Notes:

Case #4: Shelby

5-year-old, female spayed, Rottweiller
Acute eruption of pustules on ventral abdomen, neck, and face

Notes:

Case #5: Brutus

5-year-old, male neutered, Great Pyrenees
History of atopy with seasonally recurrent bacterial folliculitis. This year getting worse instead of better with same treatment protocol
Physical exam findings: Alopecia, crust, erythematous macules over entire body

Notes:

GUIDELINES FOR PYODERMA SUSPECT

My general approach to patients presenting with clinical signs consistent with pyoderma is to use history and physical exam findings to rank likely differential diagnoses, perform three diagnostic tests in exam room, outline a treatment plan, and determine what my next step will be if Plan A fails.

History

- Is the patient pruritic? Variable pruritus suggests demodicosis, dermatophytosis, erythema multiforme, or other less common dermatoses. Pyoderma, Malassezia, atopy, food allergy, sarcoptes should all itch.
- Is this an itch that rashes or a rash that itches? Most pyoderma is secondary to atopy, food allergy, or parasite hypersensitivity; these all itch first then rash! If the patient rashes without pruritus or is only pruritic when pyoderma is active, consider hypothyroidism or hyperadrenocorticism
- Age of onset? Less than one year think parasite hypersensitivity or Demodex. Between 1 and 4 years of age, anything is possible, but atopy is number one. Over 6 years of age, food allergy becomes more likely than atopy, but also start thinking hard about endocrinopathies.
- Seasonality? Definite seasonality is usually atopy or flea allergy dermatitis. Year round, doesn't eliminate atopy or flea allergy, but you get to pile on other differentials.
- Higher risk for parasite exposure? Recent adoptee in household? People or other animals in household itching? If recently adopted or a new member to household, then DTM and treat for parasites.
- Regular flea/tick control? Use all your wiles to convince and cajole them into flea prevention.
- Previous treatment antibiotics/steroids/thyroid supplementation? Response? If highly steroid responsive bump up atopy. If not steroid responsive, bump down atopy and bump up food allergy, endocrinopathies, and unusual dermatoses such as T-cell lymphoma or erythema multiforme.

Physical Exam

- Distribution? Symmetrical distribution suggests auto-immune, endocrinopathy, or systemic disease. Asymmetrical or patchy suggests dermatophytosis, demodicosis, or pyoderma secondary to hypersensitivity disorder
- Haired skin only? Demodex, dermatophytosis only affect haired skin
- Nasal planum, lips, or mucocutaneous junctions? Autoimmune disease, erythema multiforme, or drug eruptions. Demodex and dermatophytes can be ruled out.
- Concurrent signs? Look for signs of Cushing's disease, hypothyroidism, or systemic illness. Look for erosions, ulcerations, or nodules that might push you to biopsy now.

Initial Diagnostic Testing

- Four essential tests for every patient: Cytology, skin scraping, DTM, and parasite treatment trial
- If no bacteria or yeast on initial evaluation recommend obtaining DTM during first visit
- If appropriate: thyroid panel, food trial, allergen-specific testing, screen for Cushing's
- If looks serious or fails to respond to your top differential: BIOPSY, BIOPSY, BIOPSY

Initial Therapy

- Systemic antibiotic for 3 to 6 weeks. First choice for routine pyoderma: Cefpodoxime (SID), second choice is cephalexin or Clavamox (BID). Fluoroquinolones only for gram-negative pyodermas or if culture says only choice. Don't recommend fluoroquinolones as first line for routine staphylococcal pyoderma due to emerging resistance
- Appropriate shampoo/conditioner: Chlorhexidine, benzoyl peroxide, ethyl lactate. May choose to combine with antiseborrheic ingredients
- Mupirocin ointment for localized pyoderma, such as chin furunculosis or fold pyoderma
- Aggressive flea control: "Golly, this probably isn't fleas, Mrs. Johnson, but I'd sure hate for Fluffy to get fleas while we are doing all these tests to figure out what is causing her problems." Or, "Ya know, I believe in controlling the things we can. I can't control ragweed, but I can control fleas."

Recheck Examination: 2 to 4 weeks while still on antibiotic

- Ask client to score pruritus, odor, appearance of skin (scale 1 to 10).
- Repeat cytology to verify if bacteria is resolving or if *Malassezia* is present
- If good response, treat for 1 to 2 weeks beyond "cure" and proceed to maintenance therapy
- If not improving, then evaluate all causes for treatment failure listed in introduction
  - Client compliance – verify and reinforce
  - Review antibiotic selection, dosage, and interval
  - Consider culture if you truly suspect resistance
  - Repeat skin scraping and DTM to be sure you didn't miss the common differentials
  - Any time dermatitis fails to respond to appropriate therapy for current diagnosis → biopsy biopsy biopsy. Could be T-cell lymphoma, pemphigus, or erythema multiforme.

Maintenance Therapy for Pyoderma if Good Response

- Treat primary underlying disease
- Antiseptic shampoo/conditioner every 1 to 2 weeks life long
- Immune modulation therapy: Staphage Lysate (Delmont Laboratories)

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3. Scott, Miller, Griffen: Muller and Kirk's Small Animal Dermatology, 6th ed. Philadelphia: WB Saunders, 2001.
4. Campbell KL (ed.): Small Animal Dermatology Secrets. Philadelphia: Hanley & Belfus, 2004.
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Answers:

1. Bacteria, demodex, dermatophyte
2. Bacteria, demodex, pemphigus foliaceus
3. Malassezia dermatitis, flea allergy dermatitis, sebaceous adenitis, pemphigus foliaceus, erythema multiforme, toxic epidermal necrolysis, epitheliotrophic T-cell lymphoma (mycosis fungoides), superficial migratory erythema (hepatocutaneous syndrome), calcinosis cutis, schnauzer comedone syndrome, follicular dysplasia, juvenile cellulitis (puppy strangles), bullous pemphigoid, dermatomyositis, vasculitis, systemic lupus erythematosus, contact dermatitis, sun-damage, eosinophilic furunculosis, Sarcoptes, Cheyletiella, trombiculiasis, hookworm dermatitis, pelodera dermatitis, canine distemper, leishmaniasis, pythiosis, zygomycoses
4. Skin cytology, skin scrape, DTM, and parasite treatment trial
5. Biopsy (bet you thought I was going to say culture – that's number 2 unless in high methicillin-resistant Staphylococcus area)

MANAGEMENT OF THE ATOPIC PATIENT

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THERAPY

Allergen avoidance, while logical, is time consuming but can be quite helpful. Measures taken to reduce allergens in the environment will help all allergic individuals. Dust covers on the pillows, mattresses, and pet beds help keep dust and dust mites under control. Wash bedding, throws, and blankets in hot water once a week. Room air cleaners with HEPA filters are great for small rooms such as bedrooms and are relatively inexpensive. Owners can dust and vacuum once a week, keeping the pet outdoors during the cleaning process. Indoor molds are present in basements, closets, laundry, garages, and bathrooms. Keep the affected animal away from these areas if possible. Outdoor molds are present in mowed grass, mulch, dried leaves, and low ground cover. Rinse the feet and wipe the hair coat down with a damp cloth to remove accumulated allergens. It is important to remember that percutaneous absorption of pollens plays a big factor in our atopic patients. Give your clients these guidelines at the beginning of immunotherapy and as part of your treatment program.

IMMUNOTHERAPY

The long-term time commitment needed from both the owner and the veterinarian for successful immunotherapy cannot be overemphasized. It is usually for the life of the animal. The owner must be willing to follow instructions accurately, be patient, and be able to communicate effectively with the veterinarian. The veterinarian must be able to recognize and treat other primary or secondary causes of pruritus (otitis, pyoderma, *Malassezia* dermatitis, and insect hypersensitivity) as they occur.

Owners should be advised of realistic expectations **before** allergy testing or immunotherapy. This form of therapy will not cure their dog of allergies. Nothing will. The goal of immunotherapy is reduction in pruritus and leveling off of the clinical signs during allergy season. The time observed to clinical response varies from 2 to 12 months, but I ask owners to be committed to one year. Owners should expect a 50% to 70% reduction in pruritus and dermatitis with this therapy alone. Adjunctive therapy will still be needed in most cases. Allergy shots are best administered at home and the owner should be comfortable with its administration. The owner should be trained to give the injections by your professional staff, be advised of common side effects to watch for, committed to giving the injections according to the protocol, and present the pet for regular follow-up visits. If the client is reluctant to give the shots, then of course they can be administered in the clinic.

Induction

There are several protocols used for immunotherapy in dogs and cats, none of which have been tested in a controlled study. By convention, most protocols include a two- or three-vial set starting with a either a 200 or 2000 pnu (protein nitrogen units) concentration building to a 20,000 pnu maintenance solution. The maximum number of antigens in a single vaccine is typically 15. During the induction period the injections are given every 2 to 3 days until the maintenance dose is reached.

When therapy is started, the owner is advised to watch for increased pruritus or exacerbation of dermatitis after an injection is given. This reaction occurs rarely, is dose related, and the owner must consult with the veterinarian. Should this happen, the dose is reduced to the previous amount where no pruritus was observed. Conversely, a reduction in pruritus followed by an increase before the next shot is due suggests that the injections should be given more frequently. Divide the dose and give the shots twice as often.

Symptomatic therapy is required in almost every case during the induction period and at various times of the year. Symptomatic therapy includes not only antipruritic medications (glucocorticoids, essential fatty acids, corticosteroids, antihistamines, topical shampoos and rinses) but also specific antimicrobial therapy. It is also VERY important to remember that allergy shots should be modified for each individual patient. It is very important to follow up with these patients and schedule routine follow-up examinations every 3 to 4 months or more frequent if necessary.

GLUCOCORTICOIDS

The principle of use of glucocorticoids for pruritus is to **use as infrequently as possible, as low a dose as possible, and NEVER let the treatment be worse than the disease.** Only short-acting glucocorticoids are recommended. The half-life must be shorter than the interval of dosing. Drugs that can be used on alternate-day basis include *prednisone, prednisone and methylprednisolone.* Methylprednisolone has a slightly longer half-life than prednisolone and 4 mg of methylprednisolone equals 5 mg of prednisolone. Methylprednisolone drug does not cause as much polydipsia. However, it is more expensive than prednisone or prednisolone.

Pruritic patients that are to receive glucocorticoid therapy for longer than 2 weeks should be given prednisone or prednisolone on alternate days or less often. Dosages needed to control pruritus at the outset of therapy may be higher than the dosage needed for maintenance. Alternate-day therapy does not eliminate all undesirable effects of glucocorticoids, but it does minimize adrenal suppression.

The use of injectable glucocorticoids is almost never advisable in the treatment of atopic patients. With repositol forms of glucocorticoids, suppression of the pituitary adrenal axis far outlasts the anti-inflammatory duration of the drug. Some owners will report that oral medication in the dog does not work as well as injectable. This problem can be corrected by increasing the initial dose of the oral drug or changing to a different oral glucocorticoid.

An anti-inflammatory induction dose of prednisone/prednisolone is 1-2 mg/kg/day for the dog. After the pruritus is controlled, the dosage is changed to an alternate day regimen and the dose is then decreased to the lowest possible level. There are a multitude of ways to decrease the dose from daily to every other day. One approach is to take the lowest daily dose that will control the symptoms and increase it by 50%. This dose is then given every other day. This dosage can then be adjusted down. The target dose for chronic maintenance therapy should be less than 0.5 mg/kg every other day.

Animals on chronic glucocorticoids supplementation **should be monitored** every three to four months with a bacterial culture and sensitivity of the urine, CBC and chemistry panel should be evaluated once or twice yearly.

Patients on chronic maintenance therapy should be acceptably itchy, not completely itch free!

STEROID-SPARING DRUGS

Antihistamines block the classic inflammatory effects of histamine. They may also directly inhibit or stimulate mast cell secretion, may change the number, activity or both of helper or suppressor T lymphocytes, and may activate other cells such as the eosinophil that alter mast cell function. There are *six different classes* of antihistamines (H1 blockers) and a great deal of individual variability in the response to antihistamines. It is worthwhile to try two or three different antihistamines, one from each class for two to three weeks each in evaluating the efficacy of antihistamine therapy. Antihistamines are also now classified as to first and second generation. First generation antihistamines may also activate muscarinic cholinergic, 5-hydroxytryptamine (serotonin) or alpha adrenergic receptors whereas few of the second-generation antihistamines have any of these properties.

The selectivity of the second-generation antihistamines reduces central nervous system toxicity. In addition, second generation antihistamines are not able to cross the tightly fused outer membranes of the endothelial cells lining the brain capillaries. Second generation antihistamines that have been tried in veterinary medicine include astemizole, loratadine, and certirizine. Astemizole is one of the most specific H1 receptor antagonists currently available. Sedation is uncommon, as this agent binds preferentially to peripheral H1 receptor **sites rather than to central H1 receptor sites.**

The major side effect of antihistamines is sedation; this may decrease after several days of treatment. Uncommonly excitation or tremors may be caused by high dosages. Increased efficacy may be expected when antihistamines are combined with fatty acid supplementation. Individual patients may develop antihistamine tachyphylaxis after a period of time. In these instances, a different antihistamine class should be evaluated.

Fatty acid nutraceuticals, when used appropriately, may modulate the formation of prostaglandins, thromboxanes and leukotrienes. In North America, n-3 fatty acids are used almost exclusively in allergy management. Diets rich in n-3 fatty acids can result in the incorporation of n-3 fatty acids into biological membranes, with a corresponding decrease in concentrations of n-6 fatty acids such as arachidonic acid. N-3 fatty acids are converted into a leukotriene B, prostaglandin E and thromboxane A that are less pro-inflammatory than the corresponding n-6 fatty acid isomers. In this regard, the ratio of n-6 to n-3 fatty acids in the diet is important. In one study, a ratio of 5:1 to 10:1 n-6:n-3 fatty acids resulted in a decrease of the inflammatory leukotriene B4 after 6 weeks in the plasma and 12 weeks in the skin. Most diets are probably much higher in n-6 to n-3 than this ideal. For control of signs of atopy in the dog, dosing of n-3 fatty acids at 180 mg of EPA/5 kg, used with a low-fat diet, was found to result in better control of the allergic symptoms. The n-3 fatty acids are contained in cold-water fish oils. Fish oil supplements, to be useful in allergy management, should contain at least 90 mg EPA/capsule.

Pentoxifylline is a phosphodiesterase inhibitor that has a number of anti-inflammatory effects: it decreases cytokine production (IL-1, IL-6 and TNF-α) and the expression of adhesion cell molecules thus decreases the accumulation of inflammatory cells at sites of allergen challenge (late phase cutaneous reaction at 4–6 hours). Pentoxifylline suppresses contact allergy by suppression of TNF-α which is considered an important mediator in delayed-type hypersensitivity. To date, its use does not seem to have decreased intradermal skin test reactivity. It has been tried with minimal success in canine atopics at 10 mg/kg TID.

Cyclosporine works by targeting the T lymphocytes binding immunophilin thus inhibiting calcineurin which is needed to produce inflammatory cytokines. This precise targeting of the T lymphocytes inhibits the production of the numerous cytokines driving the inflammatory reaction. Unlike systemic steroids that affect every cell in the body producing numerous unwanted effects, cyclosporine only affects inflammatory cells. The recommended dose for dogs is 5 mg/kg PO daily. Cyclosporine should be given for 30 days before assessing response. If pruritus has been reduced, you may be able to reduce to every other day for the maintenance dose. The drug should be given 2 hours before or after a meal to maximize its absorption. Unfortunately, 35% of dogs suffer gastrointestinal side effects including vomiting, loss of appetite, and diarrhea. These side effects usually resolve in 2 to 3 days. Metoclopramide can be administered if necessary to help control vomiting. Ketoconazole (5 to 10 mg/kg per day) can be administered concurrently to increase cyclosporine blood levels. In these patients, the dose of cyclosporine can be reduced (approximately half) or possibly tapered sooner than in patients not receiving the combination protocol. The addition of ketoconazole is especially useful in allergic patients with concurrent Malassezia dermatitis or otitis.

TOPICAL MANAGEMENT OF PRURITUS

Topical management can be used as *adjunctive therapy* in the management of the pruritic patient. In patients with generalized disease, topical therapy is applied by means of shampoo, rinse or conditioner. *These should always be applied with cool water.* Hot baths and high ambient temperature may potentiate pruritogenic stimuli. Shampooing mechanically removes surface debris, bacterial by-products and decreases percutaneous absorption of allergens. In addition, antipruritic medications can be effectively applied topically, in many instances.

Topical antipruritic products in the formulation of *gels, creams, lotions, sprays and ointments* will be helpful in patients with localized areas of pruritus. In selecting a product for topical therapy, one must consider the vehicle the drug is combined with. For acute eruptions, the nonocclusive, nonirritating lotion, spray or gel form should be used, whereas creams and ointments are best used in chronic lesions. Ear products with glucocorticoids can also be used on the skin.

Patient monitoring is essential. A variety of perpetuating factors (pyoderma, Malassezia, otitis, fleas, etc.) are likely to occur and must be controlled as soon as they occur. I schedule owners to return at two months (when they reach the maintenance dose), 5 months, 8 months and 1 year. If all is well at each of these visits, then follow ups are reduced to once to twice a year. If at the two month visit pruritus markedly escalates after a shot, then the dose is probably too high and should be reduced to the previous concentration where no pruritus was observed. If pruritus declines after a shot but increases before the next injection is due, then the shot needs to be given more often.

FOOD ALLERGY: HOW TO DIAGNOSE AND TREAT

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CLINICAL SIGNS

The clinical signs of food allergy can be quite variable. The clinical signs are going to be nonseasonal but seasonal peaks can occur if the patient has concurrent allergies, such as flea allergy dermatitis or atopic dermatitis. The signs are almost always cutaneous but concurrent gastrointestinal signs can be seen in some patients. While the great majority of dogs with food hypersensitivity manifest pruritus of the ears and feet, the distribution can also be extremely variable. Generalized pruritus may occur but some dogs will have the classic "ears and rear" involvement. In addition, pruritus localized to the ears may be the only symptom. Both primary and secondary skin lesions can be seen. These include erythematous papules, pustules (from secondary infection), seborrhea, angioedema/urticaria, excoriations, and traumatic alopecia. There is a subset of food-allergic dogs that present with non-pruritic, recurrent pyoderma. Other less common symptoms of food allergy include gastrointestinal signs, malaise, and seizures. Although many food-allergic dogs may present with initial symptoms at less than 6 months of age, food allergy can occur at any age. In general food allergy occurs in young and old dogs.

Nonseasonal pruritus is also the most common symptom of food allergy in cats. Often, pruritus is intense, and directed around the head and neck. However, generalized pruritus can occur. Food allergy has also been implicated as a cause of miliary dermatitis, eosinophilic granuloma complex, eosinophilic folliculitis/furunculosis, and self-inflicted alopecia in cats. Less common manifestations of food allergy in cats include gastrointestinal symptoms, angioedema/urticaria, and conjunctivitis. Gastrointestinal signs may include increased defecation frequency, soft feces, intermittent diarrhea, and flatulence.

DIAGNOSIS

Food allergy can mimic other dermatologic conditions, so it is important that a minimum dermatology database has been performed. Skin scrapings, both deep and superficial, Dermatophyte Test Medium (DTM) tests, and skin cytology should be performed to rule out other pruritic dermatosis and concurrent bacterial or *Malassezia* infections. With severe pruritus, I would also recommend empirical treatment for sarcoptic mange.

The most reliable method of diagnosing food allergy and the only one recommended is a hypoallergenic dietary trial. Antigens are available for intradermal allergy testing, and some of the serum ELISA or RAST allergy tests measure food antigens. The predictability of these tests or their correlation with provocative challenge is poor. **Neither skin testing nor serologic testing is a reliable diagnostic test for food allergy and should be avoided.**

The goal of the hypoallergenic diet is to clean the animal's system out of all previously fed foods with the ultimate goal being resolution of pruritus and/or dermatitis. Owners are reminded that the food trial is a TEST conducted at home. Our goal is to find out what foods should be avoided and then return to an appropriate commercially available diet. The idea is to do it once, do it right, and get the pet on a food it can eat that does not cause it problems. This *test* is accomplished by placing the animal on a controlled, limited ingredient diet for 8 to 12 weeks and monitoring the animal for signs of improvement.

After taking a thorough dietary history, a commercial single novel protein, and ideally novel carbohydrate, diet with very limited ingredients is selected as the initial diet. Alternatively if the client is willing, a home-cooked diet using a novel carbohydrate and protein source can also be used. Alternatively, there are now commercial diets that use hydrolyzed protein sources. The hydrolysis process alters the molecular weights of the proteins to the range of 5,000–12,200 daltons in the available veterinary formulations. In general the major food allergens (in people) are in the 12,000–70,000 dalton range. The hypothetical advantage of these diets is that if the molecular weight of the protein is small enough, it will not elicit an immunologic response in patients sensitive to the original protein.

A handout describing the restrictions of an elimination diet and a diet diary are given to the owner at the start of the food trial. The owner must be advised that substitutions, additions, snacks or treats (except fruits and veggies) are not permitted during the test period. **All flavored vitamin supplements, preventative medication, and fish oil supplements must be stopped or a nonflavored version substituted during the food trial.** All rawhide chew toys, pig ears, cat food, cat feces, and so forth must be placed out of reach. Outdoor pets should be confined during the course of the trial to prevent dietary indiscretions. Even the litter box must be made unattainable to the indiscriminate canine palate. It is also very important to *switch to non-chewable heartworm preventive!* A recent study at NCSU showed that once-a-month heartworm pill (containing soy and beef) is sufficient to keep a soy-allergic dog symptomatic.

The owner is advised to record the amount of the hypoallergenic diet fed/eaten, other food fed/eaten, level of pruritus, and character of stool on a daily basis. The diary is brought to each office visit for review by the clinician. Often information not volunteered by the owner (eg, animal boarded for a week during which time pruritus increased) is revealed in the diet diary. The owner is advised that their pet should not gain or lose weight while on the diet. The truth is that many animals whose pruritus has been treated with glucocorticoids have gained an excessive amount of weight and can stand to lose. The hypoallergenic dietary trial is an excellent time to help this along.

Scheduled follow-up evaluations (4 and 8 weeks) are key to assess the pet's response and to adjust the diet as deemed necessary. A realistic expectation is a 50% improvement in about 70% of the food allergic animals after 4 weeks on the elimination diet. Because some food-allergic pets have multiple simultaneous allergies, complete resolution of pruritus may not occur. If a superficial pyoderma or fleas are present, these conditions must be treated and eliminated before a fair evaluation of the elimination diet can be made. Evaluate the pet at 4 weeks and if pruritus/dermatitis persists, continue the diet for an additional 4 to 6 weeks.

The Dietary Challenge

The dietary trial is incomplete and a diagnosis of food allergy cannot be made without provocative challenge. This is accomplished by re-feeding the previously fed commercial pet food for 7 to 14 days. The diagnosis of food allergy is made when the signs reoccur upon feeding the commercial pet food, and is confirmed with resolution of clinical signs when the elimination diet is re-fed. Most often, signsy recur within a 24- to 48-hour period. The exception to this is the patient with recurrent pyoderma. Signs may not be observed for 7–10 days after initiating the challenge. Owners are asked to make a list of the ingredients in the commercial diet. A positive reaction (itching or dermatitis) on provocative exposure of this diet means that the animal is allergic to at least one of the items on the list.

A negative reaction with exposure to the previously fed base-diet does NOT rule out diet hypersensitivity, however. It is not unusual for the offending agent to be a treat (commercial or from the table), rawhide, or dietary supplement. Owners are advised that if their pet improves during the elimination period, but does not relapse on the commercial diet than this diet can be fed as the maintenance diet. However, if an owner desires to introduce another food or treat, it must be done with the same degree of careful, monitored exposure.

The final maintenance diet is determined by how the pet reacted on challenge. Of course the challenge list is not all-inclusive, so there may be some degree of trial and error involved with finding a final diet. In addition, it is always possible that the pet may develop new allergies in the future. However, this appears to be an infrequent occurrence in adult dogs.

FELINE ALOPECIA

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Feline alopecia is a common problem seen in everyday veterinary medicine. Alopecia is defined as loss of hair and may vary from partial to complete. Various patterns can occur such as focal, multifocal, diffuse, or symmetrical. Alopecia can be congenital or acquired. It can be a primary disorder, such as seen with endocrine disorders and follicular dysplasias, or secondary to trauma or inflammation (eg, dermatophytosis, demodex, allergies). It is important to formulate an organized history and diagnostic plan to limit potential differential diagnoses. An accurate diagnosis is imperative to successfully treat the alopecia.

DIAGNOSTICS

The most important factor before the workup is started is to determine if the alopecia is self-inflicted from over-grooming or if the hair has simply fallen out. This can be determined by placement of an Elizabethan collar or the use of a trichogram. If the hair regrows when the cat is placed in an Elizabethan collar then this confirms the cat is causing the alopecia. A **trichogram** is used to visualize the hair for evidence of pruritus (self-inflicted alopecia), dermatophytosis, endocrine alopecia, pigmentation defects, and growth phase.

Performing a Trichogram

1. Grasp individual hair with hemostatic forceps and pluck hair completely (approximately 20)
2. Lay hair on microscope slide (with mineral oil) with hair oriented in the same direction.
3. Examine hairs at low power for morphology, concentrating on hair bulb, shaft, and pigmentation.

The hairs are examined for integrity of the shaft, stage (anagen, catagen, or telogen), and pigmentation. If most of the hairs have been sheared off, this is likely the result of licking, as seen in cats that excessively groom. Hair breakage is also seen in coat-dilution alopecia and traction alopecia. Damage to the shaft can be seen with several uncommon conditions, but dermatophytosis is the most common cause. When a hair bulb is present, it is important to document whether the follicles are predominantly in anagen, telogen, or catagen. Anagen bulbs are round shaped, while telogen bulbs are often spear shaped. Predominance of telogen follicles can be indicative of endocrinopathies, nutritional disorders and metabolic diseases. This is not an exact science, however, and there is a great deal of breed variability.

Skin scrapings are an under utilized diagnostic tool in feline dermatology. Demodex mites are an important cause of alopecia. Deep skin scrapes are used to check for *Demodex cati*. Superficial skin scrapes are used to try to identify *Demodex gatoi*. *Demodex cati* is a follicular-dwelling mite and has a long slender tail, similar to canine *Demodex* mites. These mites are usually seen affecting a single pet in the household. Immunocompromising diseases such as hyperthyroidism, feline immunodeficiency virus (FIV), feline leukemia virus (FeLV), and underlying malignancy should be sought as the cause of demodicosis. Treatment for the cause of *Demodex* is more important than resolving the mites. Other parasitic causes of alopecia include chiggers, lice, *Notoedres cati*, and *Lynxacarus radovski* (cat fur mite). Diagnosis is usually straightforward by use of tape preparations, magnifying lens examination, and skin scrapings.

The diagnostic value of the **Wood's lamp** is limited to a screening test for *Microsporum canis*. Negative fluorescence does not rule out *M. canis* because fewer than 50% of these infections routinely fluoresce, and is not useful for the diagnosis of dermatophytosis caused by other organisms, including *M. gypseum* and *Trichophyton mentagrophytes*.

A Wood's lamp uses ultraviolet light filtered through a cobalt or nickel oxide to cause some fungi to glow green in a darkened room. A tryptophan metabolite is the fluorescing material, not the fungi or spores themselves. This metabolite is only seen when the fungus is growing on hair shafts; it is noticeably absent on scale, claws or material growing on a culture plate. Only *M. canis* fluoresces (also *M. distortum, M. adouinii* and *T. schoenleinii* in humans), and then only about 50% of the time. Whereas dermatophytes fluoresce an apple-green color, most scales and medications glow a more blue or violet hue. The examination must be performed in a darkened room. A complete examination of the skin surface will require almost 5 minutes. If positive hairs are present, these should be plucked and used for a DTM culture. Remember that fluorescence seen on surface scale, crusts or on claws is going to be false positive. Also, since the fluorescence is due to metabolites, not viable spores or fungi, a positive fluorescence might persist even in the face of successful systemic therapy.

Dermatophyte Test Medium (DTM) fungal cultures are used to isolate and identify dermatophyte organisms. Dermatophyte Test Medium is made with special ingredients that inhibit bacterial growth and turn red when dermatophytes grow.

Performing a DTM Culture

1. Select samples for culture. Wood's lamp can be used to help select contaminated hairs or scales.
2. Longer hairs should be clipped short and the area cleaned with alcohol to decrease contaminants. Inoculate material onto Dermatophyte Test Medium. I prefer the DermDuets by Bacti-lab.
3. If media are in capped vials, be sure the caps are not tightened.
4. Keep at room temperature but in darkened environment (some recommend incubating).
5. Check cultures daily for evidence of fungal growth and color change of DTM from amber to red. A daily log should be kept. Most dermatophytes grow as fluffy white colonies. Ignore any color change that occurs after 2 weeks.

6. Examine microscopically all fungal growth for purposes of identification.

A **biopsy** may provide useful information in identifying the cause of the alopecia. It is essential to provide a thorough history and description of physical findings to the pathologist. Select lesional skin and normal haired skin, and make certain that they are identified correctly. Histopathology can be helpful in differentiating congenital/hereditary, endocrine, and telogen defluxion from allergic causes. However, in mildly inflamed, trauma-induced alopecic skin, the results may appear as "normal."

A **complete blood count** with **serum chemistry profile** is sometimes useful as a diagnostic tool for feline alopecia. Most allergic causes will have changes in eosinophilic counts but are not diagnostic alone. If there is any clinical evidence of systemic illness associated with the alopecia, then laboratory blood work is indicated.

MISCELLANEOUS DISEASES

Bacterial folliculitis is an uncommon cause of feline alopecia. When severe traumatic alopecia is encountered, a concurrent bacterial overgrowth may ensue. Cytological examination and bacterial culture make a diagnosis. A positive response to antibacterial therapy can be a helpful diagnostic tool.

Feline allergies to fleas, inhaled allergens, and food allergens are among the most common causes of alopecia. A thorough history can help to differentiate self-inflicted alopecia from spontaneous alopecia. However, some cats are secretive groomers and the owner many not see the cat lick or pluck at the hairs. Many times there is a concurrent observation of increased hairballs because of the consumption of hair

When there is a sudden onset of alopecia and other causes of alopecia are ruled out, there are some uncommon circumstances to consider. Cats with urinary tract cystitis may suddenly lick exuberantly at the caudal abdominal region. Similar findings may also be seen in cats with impacted anal sacs. For both of these entities, the traumatic alopecia may extend to the caudal rear limbs, perianal region, and proximal aspect of the tail head.

There are several causes of alopecia related to hair cycle abnormalities. **Congenital hypotrichosis** and **alopecia universalis** (Sphinx cat) is usually a simple diagnosis to make and can be confirmed with histopathology.

SEBACEOUS ADENITIS

Clinically cats present with patchy alopecia, easily epilated hair, and various amounts of erythema, scales, follicular casts, and pruritus. The definitive diagnosis is obtained only with a skin biopsy. A pyogranulomatous infiltrate invades the sebaceous glands. In some cases there may be a systemic underlying disease. Cyclosporine at 5 mg/kg may be beneficial.

ALOPECIA AREATA (AA) AND PSEUDOPELADE

This rare disease is characterized by patchy (AA) to diffuse (Pseudopelade), usually noninflammatory non-pruritic alopecia. The diagnosis is made by biopsy and histopathology. In alopecia areata lymphocytes invade the bulbus and in pseudopelade the isthmic region. Alopecia areata may spontaneously regress. Therapy (immunosuppressive drugs) is usually not attempted or not effective.

MURAL LYMPHOCYTIC FOLLICULITIS

Mural lymphocytic folliculitis (sometimes associated to follicular mucinosis) has a variable clinical picture, from mild alopecic patches, to severe hair loss, erythema and variable amounts of pruritus. It is possible that this histological pattern reflects several different diseases: initial epitheliotropic lymphoma, drug reaction, sebaceous adenitis, dermatophytosis, demodicosis, pseudopelade, FIV infection, and even food allergy. The severity of the clinical picture and the prognosis depend on the etiology. Idiopathic forms of mural lymphocytic folliculitis have been described in middle aged to old cats. Therapy with steroids or cyclosporine may be beneficial. Prognosis is poor in severely affected animals.

HYPERADRENOCORTICISM

Hyperadrenocorticism is rare in cats. Clinical signs are similar to those of dogs, with the exception of polyuria and polydypsia, which are usually absent. Cutaneous lesions include patchy alopecia, easily epilated hair, dry seborrhea with dull hair, and in some cases increased fragility of the skin, which can be torn with minor traction.

PARANEOPLASTIC ALOPECIA

This is rarely seen in cats affected by pancreatic carcinoma or, less frequently, bile duct adenocarcinoma. These patients are usually systemically ill, anorexic, and may present with vomiting, diarrhea, lethargy, and weight loss. Results of biochemical blood analysis are usually within normal range. Radiographs and ultrasound usually fail to identify the tumor. The alopecia usually starts on the abdomen and legs. The hair is easily epilated and leaves a typically smooth shiny skin. In some cases there is pruritus and excessive licking, which exacerbates the alopecia. Secondary *Malassezia* infection may be seen in the clawbeds. Histologically, there is profound atrophy and miniaturization of hair follicles and mild hyperkeratotic hyperplasia of the epidermis, with occasionally a mild lymphocytic exocytosis. The prognosis is usually poor.

ATOPIC DERMATITIS — PATHOGENESIS, CLINICAL SIGNS, AND DIAGNOSIS

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PATHOGENESIS OF ATOPIC DERMATITIS: THE OLD AND THE NEW

The pathogenesis of atopic dermatitis (AD) is complex, and incompletely understood even in humans. It is important to review what we know about the pathogenesis of AD in order to understand the logical diagnosis and treatment of this disease. Historically, the primary disease was considered to be an immunoglobulin E (IgE)-mediated hypersensitivity response to an inhaled allergen—"allergic inhalant dermatitis." The IgE produced would sensitize cutaneous mast cells; the mast cells degranulate upon further allergen exposure, with subsequent mediator release causing clinical signs. The "inhalant" nature of AD is in question, and it is possible that most allergen exposure may actually occur via percutaneous penetration. We now know that both the initial sensitization, and then the re-exposure to cause clinical signs, can occur via skin contact with the allergen.

Taking one step backwards, a major underlying immunologic abnormality in AD is an alteration in lymphocyte responses to antigens, such that there is a change from IgG production (the "normal" defense response— the one we hope to evoke with, for example, routine vaccination) to IgE production (the "allergy" response). When an animal's immune system encounters a foreign substance and an antibody response is evoked, whether the IgG or IgE response predominates is controlled by cytokines released by different subsets of helper T lymphocytes. If the IgE response predominates, this is an abnormal response, and sets the stage for allergy. Many things can potentially influence which response predominates. Modulating the IgG/IgE "balance" and returning it toward the "normal" IgG bias is the target of treatments such as allergen-specific immunotherapy.

Atopic dermatitis may not always be IgE-mediated; in fact, some authorities are even theorizing that the presence of IgE may merely be an "epiphenomenon" or marker of the true underlying immunologic disorder. In humans, about 70% to 80% of patients with AD have demonstrable allergen-specific IgE in serum or are positive on "allergy tests"; 20% to 30% do not and are NOT positive on these tests. Therefore, other mechanisms are clearly involved, at least in some patients. Some examples of other mechanisms that have been shown important in human AD, and are under investigation in animal allergy, include:

- Decreased epidermal barrier function, resulting in higher permeability of the skin to allergens and irritants;
- Epidermal cells that are more easily perturbed than those in nonallergic individuals; when disturbed, these cells release many different substances that enhance the inflammatory response;
- Reduced production of antimicrobial peptides by epidermal cells, leading to greater propensity for skin infections;
- Genetic factors—Many genetic polymorphisms have been identified in human atopic individuals, most of which have the effect of somehow augmenting the inflammatory response;
- The "hygiene hypothesis"—There is a much higher prevalence of allergy in areas of the world that are "cleaner" and have better medical care. It is thought that early exposure of children to microorganisms promotes a Th1 or nonallergic bias to the immune system, and that by limiting exposure to these organisms, this process does not occur.
- Self-trauma from scratching—This exposes molecules such as fibronectin that are binding sites for bacteria. It also releases autoallergens, and in some individuals there is actually an IgE response that develops against "self" allergens!

The allergens involved (and not involved) in AD include pollens, which are somewhat regional, although many pollen allergens are common throughout the US (eg, ragweed). House dust (one of the most common allergies in humans and certainly so in dogs) is a complex substance consisting of breakdown products from clothing, furniture, animal and human dander, molds, insect parts, and house dust mites. *Dermatophagoides pteronyssinus* and *D. farinae* are the most common house dust mites in the US. They contain the substances that are responsible for most dust allergy. Grain dust mites (also called "storage mites," eg, *Acarus, Tyrophagus, Lepidoglyphus*), which live and feed on stored grain products, may be important allergens. Some small animal patients are allergy test-positive to storage mites; this is currently an active field of investigation in veterinary allergy. Molds are found in all areas of the US in soil and decaying organic matter, damp basements, etc. There is controversy over the prevalence of mold allergy in dogs; in general, positive reactions to molds are less common in most allergy tests. Animals do not often appear to be allergic to other animal danders or to human dander. Other uncommon allergens include feathers, wool, tobacco, and furniture stuffings. Household insects may be important allergens in some areas. Substances not thought to be associated with AD in animals to date include lawn chemicals or fertilizers; synthetic rug fibers (nylon, acrylic); and most ornamental plants or houseplants.

There is strong evidence that secondary infections with staphylococcal bacteria and *Malassezia* yeast not only contribute to the discomfort experienced by people with AD, but also serve to enhance and maintain the allergic state. Although the concept of "staphylococcal hypersensitivity" appears less and less valid, it is clear that certain toxins secreted by staphylococcal bacteria can directly activate T lymphocytes, stimulate them to release pro-allergic cytokines, and perpetuate the allergic cascade. It has now been demonstrated that some dogs develop IgE-based hypersensitivity to yeast allergens. Obviously, if we have a situation where a dog is allergic to a component of the normal flora (which will always be replenished by nature), we have a serious long-term problem! Thus, aberrant reactions to normal skin organisms are frequently a part of AD. Infection alone may account for much of the discomfort in atopic pets. This becomes a critically important consideration when treating AD: identification and long term control of infections is an important part of management.

CLINICAL FEATURES OF ATOPIC DERMATITIS

History is an extremely important issue in all skin disease, but especially in diagnosing allergy, where there are some important historical clues that you may be dealing with an allergic pet. A prominent feature of atopic dermatitis is pruritus, initially unassociated with lesions. The pruritus almost always starts at 1 to 3 years of age, but the onset can be from 6 months to 6 years of age (or earlier?). It's rare for a dog to "become allergic" starting at age 7 or 8, ***except*** with food allergy, which can start at any age. The signs can be either seasonal or nonseasonal pruritus. If seasonal, over a few years, the "season" often lengthens such that it is year-round after 3 or 4 years. The pruritus may worsen from year to year. There may be changes in the degree of pruritus with changes in environment (eg, visits to friends, boarding, walks in the country).

Atopic dermatitis has strong breed predispositions in dogs (however, these are not absolute and subject to regional variation): it is more commonly seen in retrievers, terriers, Chinese Shar Peis, Boxers, and Dalmatians. If corticosteroids have been used for treatment, there is often a good response. Contrast this with diseases like food allergy and scabies, where there is often a poor response!

On physical examination, owners often say the dog itches "all over," but the worst places are classically any combination of the following: axilla, ventrum, lateral thorax, flanks; feet; and face/ears. There is typically alopecia, which is related to the pruritus and secondary complications, and can be remarkably symmetrical. Don't get confused and think of endocrine disease if a pruritic animal has symmetrical alopecia!

There is often no primary rash in atopic dermatitis. Early skin changes may be limited to just erythema. Most visible lesions are secondary to the pet's scratching, or to complicating diseases such as pyoderma, yeast dermatitis, or seborrhea. Excoriations from scratching may be seen. Secondary staphylococcal pyoderma is ***very*** common in allergic dogs, as manifested by a papular-pustular eruption, focal crusts, and epidermal collarettes. Secondary seborrheic disease is common in dogs, as is yeast overgrowth (*Malassezia* dermatitis).

Also very common is bilateral, chronic, recurrent otitis externa; in fact, bilateral itchy ears and intermittent ear infections is the major or *only* manifestation of AD in some dogs. Be sure to examine the concave surface of the pinnae: in this author's opinion, pinnal dermatitis is one of the hallmarks of AD in many patients. Recurrent "hot spots" can be a manifestation of atopic dermatitis. Some dogs and cats have ocular signs (conjunctivitis, lacrimation, rubbing at eyes), and a few have anal pruritus. Severely affected, chronic cases may have dramatic alopecia, hyperpigmentation, and lichenification. Respiratory signs are rare in dogs; cats may occasionally have "feline asthma," although so far no one has established a firm link between allergy and "asthma" in cats, as is clearly present in humans.

We know very little about AD in cats. In part, this is because "allergy testing" cats is more difficult and less well studied. The range of clinical signs seems broader than in dogs—cats can look very similar to dogs with AD, but there are also a variety of "feline skin syndromes" that have been linked to allergy, such as ventral symmetrical alopecia, miliary dermatitis, and eosinophilic granuloma.

INITIAL STEPS IN DIAGNOSIS OF ATOPIC DERMATITIS

Initially, AD is a diagnosis made clinically using the following three elements; all are *required* for a clinical diagnosis of AD:

- Compatible history
- Compatible clinical signs
- All other causes of pruritic dermatitis that can appear similar to AD have been ruled out.

The following diseases can especially mimic AD, and must be ruled out before you can make a clinical diagnosis: food allergy, flea allergy, mites (especially *Sarcoptes*, *Cheyletiella*), pruritic staphylococcal pyoderma due to some other cause, and primary yeast dermatitis. A typical diagnostic evaluation for a potentially atopic patient might therefore include (the order of tests depends somewhat on the case): good history and examination; skin scrapings to help rule out mites; skin cytology to find bacteria and yeast; flea control if fleas are seen or suspected; a hypoallergenic diet trial; treating pyoderma with antibiotics if it is suspected or present; treat for scabies; treat for yeast dermatitis if suspected or present. Diagnostic tests that are of limited value for atopic dermatitis include CBC and chemistries, which should be normal; a skin biopsy ("nonspecific" pattern of inflammation); and endocrine tests, which are normal.

It is very important to understand that atopic dermatitis is a *clinical diagnosis*—it is made using clinical observational skills and elimination of alternative differential diagnoses. AD is *not* diagnosed by use of an "allergy test." Allergy tests are useful only to *plan immunotherapy* once you are sure the patient is allergic.

ATOPIC DERMATITIS — IgE TESTS VERSUS ALLERGY TESTS

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THE TRUTH ABOUT "ALLERGY TESTS"

The use of a confirmatory "allergy test" is commonly considered in the diagnosis of atopic dermatitis (AD). The first and most important thing to understand about "allergy testing" is that *no allergy test is perfect.* Allergy tests of different types have varying sensitivities and specificities, and ALL types have (to a greater or lesser extent) "false negatives" and "false positives." Therefore, allergy tests do not answer the question "is this pruritic patient allergic?" You cannot simply apply these tests to an itchy patient for the purpose of initially diagnosing allergic disease, because some patients with other itchy diseases will also be positive. A striking example is in canine scabies, where the presence of the scabies mite evokes an allergic response that may cross-react with other mites. Dogs with scabies can be highly positive on an allergy test to house dust mites, which could obviously lead to a rather serious error in diagnosis and treatment! Rather, allergy tests answer the question "in this patient for which I have already made a **firm** clinical diagnosis of AD, to which substances is he/she allergic?"

WHY AND WHEN TO TEST?

Why, then, consider performing an allergy test? The major reason to perform an allergy test of any type is NOT to diagnose the disease. *The reason is to allow the clinician to select allergens for use in allergen-specific immunotherapy…period!* Identifying the specific allergens to which a patient is sensitive may also enable the owner to pay closer attention to environmental factors that contribute to allergen exposure. In addition, some owners just plain want to know what their pet is allergic to! Consider, however, warning the owner of the fact that virtually never do we find a cat or dog is allergic to something that can be easily removed from the pet's environment.

When should you allergy test? Again, the first answer is "after you have already diagnosed allergy." That aside, there has been demonstration that the results of allergy testing can vary throughout the seasons. This is not true with every dog, in every situation; however if you have to choose a time to allergy test, the best time would be just after the pet has been exposed to every pollen and dust allergen for that season. In cold-weather areas, this means that allergy testing is best done in the late summer to fall, just after everything is done pollinating. In this case, the allergic response will be maximally "cranked up" to as many allergens as possible. As an example, a pollen-allergic pet may be highly symptomatic in May. But in May, it's been 10 to 11 months since that pet's immune system has been exposed to June and July pollens…so in theory, it's a *bad* time to test. These principles are in part theory, and will vary with climate and with individual pet. The age of the pet may also influence the decision to test. The author has tested many 1-year-old dogs with dramatically positive allergy tests. However, one also sometimes sees that young animals are negative on testing, but on repeat testing a year later they are highly positive. Thus, I always warn owners of very young animals that there may be a slightly increased chance that their pets will be negative.

PRINCIPLES OF ALLERGY TESTING

It is useful to examine the different principles on which allergy tests rely. Intradermal testing (IDT) is the method of choice for many specialists in veterinary dermatology and allergy. Intradermal testing has the advantage that it is a biological method that in some ways mimics the pathogenetic mechanism of the actual disease. A positive intradermal test requires not only presence of specific IgE antibody, but functional mast cells and microvascular response. With the notable exception of house dust mite allergen, intradermal testing appears to be relatively free from positive reactions in nonallergic dogs. It is also considered by some authorities to be more sensitive than serum-based methods. There are important drawbacks to IDT, the most obvious of which are its requirement for referral, and for discontinuation of treatment for weeks to months prior to the test. Being dependent on a biological system, results of IDT are subject to multiple other influences such as stress, concurrent disease, and presence of inflammatory skin lesions. Also, it is clear that some animals with strong clinical signs of AD are negative on IDT—again, it is not a perfect test.

In vitro testing methods (serum-based tests) are increasingly used both by specialists in veterinary allergy and by general practitioners. When done reliably and used properly, these tests are very valuable tools to use in formulating an immunotherapy prescription. These are "IgE Tests"—they measure *only* the amount of allergen-specific IgE present in the serum, and *not* whether this IgE is functioning to cause an allergic reaction in a pet. These tests do not prove cause and effect. In using serum-based tests, we are assuming that if allergen-specific IgE is present, it is capable of causing allergic signs, but this is not necessarily true! As is now hopefully clear, it is certain that *"there's more to allergy than just IgE."*

Generally, in vitro methods are convenient and accessible, but in some cases seem to lack specificity: with this test, the big problem may be "false positive" reactions. Some people call these "clinically insignificant true positives" because the animal may actually have serum IgE against one or more allergens, but without clinical significance. One strong advantage of the serum allergy tests are that they are unaffected, or at least less affected, by therapy. Antihistamine treatment will make an IDT completely negative, but has no effect on serum tests. With regard to corticosteroids, several laboratories recommend withdrawal of therapy for a time period before serum testing. This author believes that there is no clear evidence that use of medications such as corticosteroids meaningfully affect serum test results.

Although these serum-based methods have much to offer—especially when referral to a specialist is not possible—they must be used and interpreted cautiously.

WHICH TEST IS BEST?

It is useful to examine some of the components of different serum-based tests so that we might understand some of their advantages, disadvantages, and how they might be changing over the coming years.

- First, radioallergosorbent testing ("RAST") is no longer used; all tests performed today are based upon safer (nonradioactive) ELISA methodologies.
- Second, all assays depend on binding of serum antibodies from the patient with allergen. Whether this binding occurs on a solid substance, such as with conventional microplate ELISA or Western blot, versus in a liquid solution (solid-phase vs. liquid-phase assay), 'might' have some bearing on the results, as the allergen molecules might be more 'accessible' to the antibodies if they are floating in solution rather than bound to a solid. However, this benefit remains only a theoretical possibility in veterinary allergy diagnosis. This particular aspect of serum testing also seems less likely to influence its end result.
- Third, allergenic extracts can vary in their content substantially from manufacturer to manufacturer, and to a lesser degree from lot to lot. This could have profound implications on the results of a serum test, and perhaps even more impact on immunotherapy results. Although allergen standardization is progressing rapidly in the human field, allergenic extracts standardized for humans may or may not have any relevance to veterinary allergy, because the specific allergenic components of the extract (the major allergens) may differ between animals and humans. Standardization of veterinary allergen extracts is technologically possible, but the extreme cost of such an effort will limit our progress in this area.
- Finally, all serum-based assays depend on a detection reagent to specifically bind to and detect IgE, without detecting any other antibody class such as IgG or IgM. Monoclonal antibodies, polyclonal antibodies, and recombinant IgE-receptor fragments are the three detection reagents in use currently. In theory, this element of the test is one of the most critical in assuring sensitivity and specificity.

One general comment that can be made about *all* serum-based methodologies (and, indeed IDT as well) is that studies have concluded that these tests are *very poor choices* for diagnosing food allergy, and really should not be used. Even in humans, they are not very sensitive or specific. As another example, we know that food allergy does NOT always involve IgE-mediated processes. Therefore, even if we did have a perfect "IgE test" for food allergens (which we do not), this test would still be inaccurate for use in diagnosing food allergy.

So, which serum-based test method is best? In large part, that depends on what is meant by "best!" To elaborate:

- If we use "response to immunotherapy" as our criterion for evaluating success, among commercial serum testing companies, no method has been conclusively shown to be better than any other. The studies have simply not been done.
- If we use "correlation with IDT" as our criterion, no method has been shown superior; moreover, use of IDT as a "gold standard" can be questioned on theoretical grounds.
- If we use "technical performance" (issues such as repeatability, occurrence of false-positive reactions) the picture is slightly clearer. In a recent study, several "negative" (nonallergic) samples were sent in triplicate to five commercial serum allergy-testing laboratories in the US. There were substantial differences between laboratories in the number of positive reactions reported, and the repeatability of such reactions. This preliminary information suggests that quality control measures may vary substantially between commercial laboratories. This subject is deserving of additional study in the future.

Overall, if both are available, should one ideally use an IDT or a serum-based test? Again, neither test is perfect. With either IDT or serum-based testing, it is clear that nonallergic animals sometimes have positive test results, and that some allergic animals seem to have negative tests. In an ideal world, performing both tests probably gives the most information on a patient's relevant sensitivities, but cost considerations usually preclude this.

Point-of-care or in-clinic "screening tests" provide an alternative and interesting approach to allergy diagnosis. These rapid, inexpensive tests detect the presence of serum IgE directed against a mixture of common allergens, and a positive reaction in one screening test (E-Screen®, Heska) was recently highly correlated with positive reactions on IDT or more extensive serum-based panels. Hence, in theory they could be used to cost-effectively select which animals would be candidates for further testing. At this writing, such screening tests are only available in Europe.

MY LIST OF COMPLETELY UNSCIENTIFIC, UNFAIR, AND EMPIRICAL HINTS FOR INTERPRETING SERUM ALLERGY TESTS

The following list of hints is based on the author's clinical observations, impressions, and experience rather than scientifically proven fact, so use at your own risk!

- An IgE test is not a serum chemistry. There are no carefully established uniform standards and controls, or normal ranges. Don't take any value to be an undeniable truth. *You must always ask yourself "does this result make sense with the patient's clinical picture?"*

- Monosensitization (allergy to only one thing) exists commonly with house dust mite—some pets are dust mite sensitive only. It does NOT exist commonly with pollens. If you have only one or two pollens very positive, caution—these may not be significant, or at least they don't tell the whole story.
- Certain pollen extracts have a reputation for being "sticky" when used in ELISA assays, and seem to generate a larger number of "false positives." As you do more and more tests, you will get a feeling for this. Ask the lab if this might be going on.
- Mold spore allergy is not common. Most dogs positive on serum-based tests to molds are negative on a confirmatory IDT. This author believes that many mold-positives are not clinically significant.
- If you do have a dog with positive mold scores, make sure you've tried antifungal therapy. I believe in some cases, mold-positives are correlated with *Malassezia* hypersensitivity.
- If you do get a test result back that doesn't seem to make sense with the patient's clinical picture, don't just forge ahead with immunotherapy. It's expensive and long-term, and you want everything going for you if the owner's going to commit to it. If something doesn't seem to tell the whole story, make sure you've done a diet trial—could there be concurrent food allergy? It is very common that we will do an IDT to confirm suspicious or "borderline" ELISA test results—consider referral for an IDT.
- Use the expertise of your lab! They are generally very good at keeping all these things in mind, and providing appropriate immunotherapy recommendations, but if you question something, call their technical service advisors and ask.
- Invest a small amount of money in your own quality control. The next few pets you allergy test, take some extra serum and save it in the fridge. If you get a positive test, send the extra serum in under a fake pet's name. You should get *roughly* the same result. Don't expect it to be a perfect match. If the result is *dramatically* different, question the quality control standards of the lab.
- If you are really, really good at clinical diagnosis of AD, and you send serum samples in for testing, about 75% should be positive and 25% negative. If 100% are positive, you are probably dealing with a lab that is giving you some false positives.
- Don't charge an arm and a leg for allergy testing. Keep it cheap, so you can offer immunotherapy to as many clients as possible. This is not only good medicine, but good business!

ATOPIC DERMATITIS – DEVELOPING A MANAGEMENT PLAN

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Atopic dermatitis (AD) is a complex, lifelong disease with many potential manifestations, and many possible modes of treatment. Treatment approaches must be individualized and flexible, combine several modes of therapy, and be aimed at both the primary disease and at secondary complications, to maximize success and client satisfaction. Within this "integrated approach," we see each of the potential therapy possibilities as "tools." Our goal with each patient is to find just the right combination of tools to provide lifelong therapy that is effective, affordable, convenient, and with as few adverse effects as possible.

Important elements of this approach include client counseling, the "pruritic threshold" concept, decreasing allergen load, decreasing pruritic load, use of medical treatments for short-term (and if necessary, longer-term) relief, and use allergen-specific immunotherapy if possible for potential long-term control.

CLIENT COUNSELING

Clients need to be told explicitly: *there is no cure for allergy!* Atopic dermatitis is a lifelong, controllable, but not curable disease. Owners should expect that things will not go perfectly—there will be relapses and secondary problems, and they should plan on higher-than-normal medical care costs over the patient's life. Also, because no one treatment is universally effective, it always takes time and experimentation to find the ideal treatment combination for the individual pet. Telling the client these facts may help to minimize the "clinic-hopping" that so often occurs with AD patients.

THE PRURITIC THRESHOLD CONCEPT

This general treatment concept holds that, in any given patient, a large variety of clinical factors are adding together to eventually push this animal over the "pruritic threshold" and result in severe clinical signs. The idea, then, is to identify and treat every possible factor that is contributing to the patient's discomfort. Factors to consider include:

- Seasonality of allergens – the management plan may be different during different parts of the year.
- Many animals have more than one type of allergy. Patients with AD sometimes have food allergy as well, and may be especially prone to flea allergy dermatitis if exposed.
- Secondary staphylococcal infections are common in AD, and contribute strongly to pruritus.
- Secondary yeast overgrowth is common in AD, and contribute as well.
- Secondary seborrhea is common, and not only augments pruritus, but facilitates infection and creates scaling, odor, and other unpleasantries for the owner.
- Secondary otitis externa is common – don't forget to specifically address the ears, if they are an issue.
- Any itchy disease is worse during hot, humid weather. Expect worsening in this case.

DECREASING ALLERGEN LOAD

Avoiding Pollen Allergens

Very few studies, even in people, address the success of pollen-avoidance measures. In part, this is because the important allergenic pollens are light and windborne, traveling many miles, and pollen avoidance is nearly impossible. Physician allergists generally recommend measures such as keeping windows closed (use air conditioning instead), minimizing outdoor activities during the morning hours when pollen counts tend to be higher, and avoiding freshly cut grass. With perhaps the exception of the last item, these measures are largely impractical in pets. Restriction of pollen-allergic pets to indoors may help, along with bathing or washing of the feet after outdoor exposure.

Avoiding Dust Mite Allergens

An entire industry is built on mite allergen reduction, from special mattress covers, to chemical house treatments, to cleaning services, to special vacuum cleaners and air filters. For severely dust mite-allergic pets, does environmental modification ("dust mite abatement") help? Dozens of studies in dust-allergic humans demonstrate that dust mite abatement measures can measurable reduce the amount of mite allergen in the household. However, the evidence for clinical effectiveness of these measures is limited and controversial, and just because you reduce the mite allergen doesn't mean the patient gets better!

In one canine study, the houses of mite-allergic dogs were treated with an acaricidal chemical (Acarosan Spray) every 4 to 6 weeks, until the results of a dust mite allergen test of the house were negative. During this time, the pets themselves received no treatment. About half of the patients in this study experienced benefit, but because the study was an uncontrolled trial, the results are a little difficult to interpret. This study is encouraging, but more work needs to be done before we can make a definitive recommendation to our clients. Importantly, to this author's knowledge, none of the products for environmental control sold in the US have been evaluated for their efficacy with atopic pets.

Avoiding Food Allergens

According to the literature, up to 13% of dogs with AD may also have concurrent food allergy. Therefore, as part of your exploration of the best management plan for each patient, it is always wise to try a hypoallergenic diet trial for at least 6 to 8 weeks to see if additional improvement results. No one diet or type of diet has been proven best for this purpose; either a novel protein or hydrolyzed protein diet should suffice. The most important concept here is that the diet trial needs to be strict. The recent wide availability of hypoallergenic dry and canned foods, treats, and chews make it much easier for clients to be compliant.

Preventing Allergen Penetration

Many humans with AD have decreased cutaneous barrier function. This leaky barrier allows easy passage of allergens and irritants through the epidermis. Strengthening this barrier function may thus help to reduce clinical signs. In humans, the primary method of accomplishing this is through application of emollient topical preparations, which is demonstrably effective. In pets, there are no published studies on topical products aimed at enhancing barrier function, but some companies are beginning to imply in their marketing literature that the product may have such an effect. We await careful studies before making any conclusion or recommendation.

It has been determined that canine skin cells, when cultured in vitro with certain nutrients, increase their synthesis of ceramides and lipids, which are components of the epidermal barrier. When these same nutrients are incorporated into dog food (Waltham Skin Support™), feeding this diet will measurably improve barrier function. The full clinical benefit of such "dietary therapy" has not been explored. Such diets are not miracles, but they may improve clinical signs in some patients.

DECREASING PRURITIC LOAD

Staphylococcal Pyoderma

Decreasing pruritic load begins with ensuring that good parasite control measures are in place. Following this, one MUST pay attention to the possible contribution of staphylococcal infection. Recurrent pruritic superficial staphylococcal pyoderma is extremely common in atopic dogs, and must be controlled as part of treatment. It is important, in each patient, to determine what portion of the overall itch is related to staphylococcal infection. This can only be evaluated by treatment with antibiotics alone for a period of time and monitoring the response. It is neither necessary nor desirable to use corticosteroids concurrently for this purpose, as their use may delay resolution of infection and will confound your ability to judge response to antibiotics. For animals where staphylococcal infection is an important and frequent source of discomfort, longer term treatment options include frequent chlorhexidine shampoos or conditioners, 2% mupirocin cream for localized areas, and intermittent use of oral antibiotics.

Yeast Overgrowth (*Malassezia* Dermatitis)

Dermatologists are increasingly recognizing the importance of "yeast overgrowth" (*Malassezia* dermatitis) as a contributing factor to atopic dermatitis, particularly in dogs. Always check for presence of yeast cytologically, and if present along with typical clinical signs (greasy or moist skin with severe pruritus that often does not respond to glucocorticoids), treat with an oral antifungal agent such as ketoconazole, fluconazole, or itraconazole (5–10 mg/kg once daily for 5–10 days). If the itch begins to decrease, it may be necessary to continue treatment for and additional 1 to 3 weeks to produce maximum relief; this is not always necessary and must be individualized per the patient's response. If the pet responds to an antifungal treatment trial, topical therapy may be used to treat and/or help prevent future recurrence. Maintenance treatment with 1% to 2% ketoconazole shampoo or cream, or ketoconazole-chlorhexidine/miconazole-chlorhexidine shampoos, rinses, or wipes is sometimes effective for prevention of recurrent episodes.

A new line of topical products (Douxo™) contains the ingredient phytosphingosine. This substance is a component of the epidermal barrier, inhibits bacterial growth, inhibits yeast, and has some interesting in vitro anti-inflammatory action. The author has found these products to be useful for some dogs with AD.

Atopic Otitis Externa

Atopic otitis externa (dogs or cats) is common as part of AD, and for some animals is a major manifestation of the disease, and deserves specific attention if present. Chronic inflammation of the ear canals results in oversecretion of cerumen, overgrowth of normal yeast and bacterial flora in the ears, and eventually ear infection. Cytology is mandatory to identify the state of the ears initially, and to plan for treatment of any infection that is present. Following resolution of bacterial infection and/or yeast overgrowth, many atopic pets benefit from periodic use of corticosteroid-only ear drops along with periodic cleaning with an ear product with residual antimicrobial action.

MEDICAL MANAGEMENT OF THE PRIMARY DISEASE

Antihistamines

Medical management of the AD should begin with the safest drugs to administer longer-term. Antihistamines may benefit 5% to 20% of pets, and they are always worth trying, though actually there is very little evidence that they are beneficial. Several should be tried for each patient. Good choices in dogs include diphenhydramine or hydroxyzine (2 mg/kg BID-TID); in cats, benefits have been seen with chlorpheniramine (2 mg/cat BID-TID) or fexofenadine (7.5–15 mg/cat, depending on size of cat, given BID). Combination with anti-inflammatory fatty acid supplements may provide additional benefit. There is no evidence that the newer, nonsedating antihistamine drugs now commonly used in human allergy have any additional benefit for animal use.

Anti-inflammatory Fatty Acid Supplementation

The "omega-3 and omega-6" anti-inflammatory fatty acids have been shown beneficial for some patients with AD. Most uncontrolled studies report 20% to 30% efficacy, and their effects seem to me relatively mild and of most benefit in early disease. The most important factor here is that the pet should receive a minimum of about 30 mg/kg/day of the anti-inflammatory fatty acids. There is no proven clinical effect of the "ratio" of these fatty acids in AD. Recently, pet food companies have increased the amount of fatty acids that are added to certain pet foods, including those intended for amelioration of skin or joint disease. In some cases, the amount of fatty acid present in these diets far exceeds "oral supplementation" levels. Therefore, if the pet eats one of these diets, supplementation with capsules or liquids is not necessary. Providing fatty acid therapy as part of the diet may be more cost-effective, more convenient, and assures that the pet receives the fatty acids consistently. Unfortunately, it is not always easy or possible to ascertain the amount of anti-inflammatory fatty acids present in a particular food by examination of the label. Hopefully, in the future pet food manufacturers will provide this information explicitly so that we can know which foods to recommend.

Even when fatty acid supplementation does not appear to benefit a patient on its own, it may be beneficial as part of combination therapy. Synergistic effects with both antihistamines and with corticosteroids have been demonstrated. As an example, if corticosteroids are the only thing that provides relief for a pet, or is the only treatment an owner can afford, concurrent fatty acid supplementation by capsule or through the pet food may help to decrease the total amount of steroid required to provide control.

Corticosteroids

Atopic dermatitis is generally quite responsive to corticosteroid drugs. They may be preferred for older animals that may not live to benefit from immunotherapy, or pets with highly seasonal disease. The chief disadvantages of longer-term use of corticosteroid drugs include development of steroid resistance or "tachyphylaxis," and adverse effects (of both annoying and medically-serious varieties). Oral prednisone or prednisolone (0.5–1 mg/kg/day, decreasing to every other day) is much preferred to other more potent drugs, or to injectable drugs, for reasons of longer-term safety. Concurrent use of the fatty acid supplements (as above) may decrease the required steroid dose. Animals receiving longer-term oral corticosteroids should have a urine culture performed twice annually to identify silent urinary tract infections. It is wise to check liver enzymes annually; elevation in serum alkaline phosphatase is expected and does not imply hepatotoxicity. Elevation in serum ALT or AST suggests progression of the effect and development of steroid hepatopathy.

Topical low-concentration (0.015%) triamcinolone spray is a relatively new corticosteroid formulation approved for canine use in the US (Genesis™, Virbac). In Europe, more recently a topical hydrocortisone aceponate spray has been approved (Cortavance™, Virbac). The latter corticosteroid is metabolized entirely in the skin, and is not absorbed into the systemic circulation, thus sparing the pituitary-adrenal axis. These solutions can be used for "trouble areas" of atopic dermatitis, such as the ventrum, feet, or anal area, or can be sprayed over broader areas of the body. The major advantage of these products is good (sometimes great) efficacy with lack of systemic corticosteroid side effects. They also may work even in patients where other corticosteroid formulations have failed. It is important not to over-apply the spray; use only enough to make the skin slightly damp without "runoff." The triamcinolone product is licensed for use for 1 month at a time; with prolonged continuous use, some animals may develop cutaneous atrophy or calcinosis cutis.

Cyclosporine A Modified (CsAM) and Other Calcineurin Inhibitors

The original cyclosporine A drug has been used for dozens of years as part of immunosuppressive therapy for organ transplant patients. The calcineurin inhibitors work by inhibiting production and action of cytokines, and through other mechanisms as well. More recent clinical trials of cyclosporine in dogs with AD demonstrate that this drug has efficacy equal to that of oral prednisone. Only the "modified" version of this drug (Atopica™, Neoral™, and generic forms available) should be used in dogs, as it is much more reliably absorbed. These preparations are the same drug, but microemulsified in a special vehicle to aid absorption. The starting dose is 5 mg/kg/day, which can be given as a single dose or divided into multiple doses. Ideally, CsAM should be given without food, as this will enhance absorption. Improvement occurs gradually, usually beginning after 1 to 2 weeks of administration and reaching maximum at 4 weeks. Thus, the initial trial should be 4 weeks. If the drug is effective, gradually reduce the dose over a period of several weeks to the minimum required for relief. Some patients will require the full starting dose long-term; others can be reduced to 50% or even 25% of the original dose for maintenance.

Perhaps 25% of patients will have some initial gastrointestinal discomfort from CsAM. In most cases, this will abate within a few weeks. Therapy with CsAM is remarkably free from long-term adverse effects. Patients on therapy do not seem to develop infections with greater frequency than other atopic animals. Gingival hyperplasia is a known adverse effect of longer-term, higher-dose CsAM therapy, but occurs only rarely at the doses typically necessary for AD. Protocols for combination of CsAM with ketoconazole for AD have not been developed. A major concern here would be potential for development of hepatotoxicity with long-term ketoconazole treatment. Concurrent administration of corticosteroids should be absolutely avoided for more than a few weeks. The combination of CsAM and corticosteroid has been associated with development of fatal opportunistic fungal infections.

Therapeutic monitoring (serum chemistries, blood counts, or CsA serum concentrations) is neither recommended nor necessary when using CsAM for AD patients. The drug works great in atopic cats as well, but is not approved for use in this species.

Cyclosporine is a large molecule, and is not readily absorbed through the epidermis. Other calcineurin inhibitors have been developed that are smaller, and active topically. Tacrolimus (Protopic™, Fujisawa) is the most commonly used of these topicals. Topical tacrolimus cream is very effective at controlling inflammation in human AD. Its use is limited in animals due to both the difficulties with using cream preparations on haired skin, and to its very high cost.

ALLERGEN-SPECIFIC IMMUNOTHERAPY

Allergen-specific immunotherapy (ASIT; formerly called “hyposensitization” or “desensitization”) is a treatment for atopic dermatitis in dogs and cats wherein extracts of allergens to which the patient is sensitive are injected, in gradually increasing amounts, to lessen or reverse the hypersensitivity state. Various theories as to how ASIT works have been advanced. The “blocking antibody theory” was popular for many years, but has been largely replaced by the “helper T lymphocyte subset” theory. This theory holds that subsets of T lymphocytes exist, one of which when stimulated evokes IgG production (Th1 response), and one of which evokes an IgE response (Th2 response). In an atopic state, the pro-allergic, Th2 response predominates instead of the more ‘normal’ or appropriate Th1 response. By administering large doses of the allergen extract, the balance between Th2 and Th1 is shifted back towards Th1. ASIT has a strong advantage of being nearly free of adverse effects in the great majority of dogs and cats, even with prolonged use. Disadvantages include the fact that it takes several months or more to begin working, that it does not always work, and that it may be relatively expensive.

Most effects of ASIT are thought to be allergen-specific, rather than nonspecific. Thus, accurate testing to identify the offending allergens in each patient is of paramount importance to successful immunotherapy. In particular, the clinician must strive to avoid ‘false positive’ allergy test results, which would result in including an allergen in the patient’s mixture that is not relevant to that individual’s disease.

Selection and formulation of an ASIT mixture is both an art and a science. Experimental observations that large doses of allergen evoke Th1 (IgG) responses and small doses of allergen evoke Th2 (IgE) responses suggest that there is some minimum, fairly large dose of each allergen necessary in a mixture to achieve benefit. Thus, many allergists limit the number of extracts used in each prescription to between 10 and 15 substances. When a large number of positive reactions are obtained with allergy testing, choosing the proper 10 to 15 substances can be based on the following: strength of the positive reaction; degree of possible exposure of the animal to the substance; consideration of patient characteristics; and botanical interrelationships of pollen allergen groups. Because proteolytic allergens present in mold extracts can degrade some pollen allergens, some allergists administer mold allergens by separate injection. Fortunately, commercial testing laboratories are knowledgeable about the details of formulating ASIT prescriptions and provide guidance.

The exact protocol and schedule for injections will vary according to the allergen preparation; generally, the extract manufacturer will provide an appropriate schedule. In some situation, particularly with very small animals or where the allergen mixture contains larger amounts of only a few allergens, the animal may not be able to tolerate the maximum specified dosage. In this case, the dosage may have to be reduced to between one half and one tenth of the normal full dose. Injections are given year-round, and the minimum initial trial period should be 12 months. As far as is known, concurrent treatments with antihistamines, fatty acid supplements, or low-dose glucocorticoids will not interfere with response. Many dermatologists now use CsAM initially with ASIT, though this can be questioned on theoretical grounds. Treatment is generally considered lifelong, though it is possible to attempt discontinuation after 2 to 3 years of injections if the animal has responded very well. If the owner stops giving the injections, then wishes to restart, the injection amount should be reduced and gradually increased again.

Expected response rate to immunotherapy is approximately 60% to 70% “good-to-excellent” response (defined as at least 50% improvement in clinical signs). Response can be seen as soon as 1 month, but more typically takes 3 to 6 months to occur, and the maximum response may take 1 year or longer. Adverse reactions to allergen immunotherapy include localized itch at the injection site and transient worsening for 12 to 24 hours after the injection (~10% of patients). Generalized anaphylaxis occurs in less than 1% of dogs and cats; such reactions are generally mild and further reaction can usually be prevented by pretreatment with an oral antihistamine 1 to 2 hours prior to each injection.

DISORDERS OF CORNIFICATION: TREATING THE SCALING BEAST

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Seborrhea is a clinical syndrome that results from some transient or permanent disruption in the process of cornification. Seborrhea is a common secondary complication in many canine skin diseases; in this case, it's a clinical sign, not a diagnosis. Seborrhea also exists in several primary forms, where it is reasonable to make the diagnosis of "primary seborrhea." The owner complaint of an "odor to the coat that cannot be washed off" is often a good indication of the presence of seborrhea.

PATHOGENESIS OF SEBORRHEA

Cornification is an extremely complex process of division and differentiation of the skin's epidermal cells (keratinocytes) to form a tough, impermeable barrier to the external environment. This barrier functions to prevent fluid loss, prevent water movement into the body, provide mechanical protection against trauma and irritants, prevent ultraviolet (UV) light damage, prevent drug and toxin absorption, and many other functions. It consists of an orderly process of cell division, cell maturation, and cell desquamation. Disruptions in any step of this process result in increases in the number of cells being formed and desquamated, and abnormalities in the lipid content of the skin. Clinically, this is recognized as scaling, crusting, and an oily or waxy feel to the skin.

The pathogenesis of seborrhea is complex and not completely understood. Most studies have confirmed that there are at least three abnormalities that are found in the skin of ALL seborrheic dogs, whether primary or secondary:

- An increased mitotic rate of epidermal cells; the epidermal turnover time (time it takes a cell to traverse from the basal cell layer up to the surface and then be shed off) accelerates from 20 to 25 days normally to 3 to 5 days in seborrhea
- A change in the composition of skin surface lipids; normally, there are few or no free fatty acids in the skin lipid. In seborrhea, the percentage of free fatty acids increases, leading to irritation and inflammation of the skin. These substances are also degraded by skin microflora, leading to a musty or yeasty odor that reappears soon after bathing.
- A shift in bacterial flora in seborrheic skin. Aerobic bacterial counts (normally about 100 organisms/square cm) rise to more than 10,000/square cm. Additionally, there is a shift from nonpathogenic micrococci to coagulase-positive *Staphylococcus*. This accounts for the frequent bacterial pyodermas seen along with seborrhea.

CLASSIFICATION AND UNDERLYING ETIOLOGIES OF SEBORRHEA

Secondary seborrhea refers to seborrhea secondary to some definable underlying cause. Nearly any insult to a dog's skin, if it persists long enough, can result in seborrhea. *Most seborrhea seen in clinical practice is secondary.* Causes to consider include allergy (atopic dermatitis, food allergy, flea allergy); parasites (fleas, scabies, demodicosis, cheyletiellosis, lice); endocrinopathies (mostly hypothyroidism); metabolic disease (almost any type); nutritional problems (poor diet, malabsorption/maldigestion, zinc-responsive dermatosis); or neoplastic disease such as cutaneous T-cell lymphoma.

Primary seborrhea refers to seborrhea that occurs without a definable underlying cause; it is related to inherent defects in the epidermal cells themselves and may involve hereditary factors. This is most common and familiar in certain breeds, such as the cocker and springer spaniel, West Highland White terrier, Chinese Shar pei, and others.

In addition to primary versus secondary, some dermatologists like to classify the disease as oily versus dry seborrhea. In oily seborrhea, the skin has a waxy or greasy feel, the dog feels "dirty," odor is more prominent, and the scaling is off-white to yellow, moist, and adherent. In dry seborrhea, the odor is less, and the scaling is often finer and whiter, and comes off easier; this is analogous to "dandruff" in human beings. This is a fairly artificial separation, and really only useful for planning topical treatment.

DIAGNOSTIC EVALUATION OF SEBORRHEA

In diagnostic evaluation of seborrhea, the most important determination to make in an animal—the initial aim—*is to determine whether the seborrhea is primary or secondary.* Initial diagnostic workup consists of assuming the seborrhea is secondary, then making a list of all reasonable differential diagnoses as to underlying causes, and ruling them out one by one. Such evaluation may include, depending on the clinical signs, skin scrapings, empirical treatment for mites, fungal culture, allergy evaluation, a hypoallergenic diet trial, thyroid evaluation, and evaluation for underlying systemic disease (complete blood test [CBC], chemistries, urinalysis). Animals with any evidence of concurrent gastrointestinal disease should be evaluated for digestive problems. While doing these initial evaluations, you should at the same time be treating the pet for secondary complications such as staphylococcal pyoderma or yeast dermatitis, which are nearly always present.

Skin biopsy with conventional histopathology is an extremely valuable and underused diagnostic technique in seborrhea. It can give indications as to whether seborrhea appears to be primary or secondary, and may also give clues to the underlying disease in secondary seborrhea. In addition, it is the ONLY test that will definitively diagnose some of the rarer, defined syndromes that create severe seborrhea such as mycosis fungoides (cutaneous lymphoma). Punch skin biopsies (6 mm) should be taken of several representative areas and ideally sent to a veterinary dermatopathologist. It is important to clear up secondary infections BEFORE biopsying a seborrheic patient. The infections themselves evoke such an inflammatory response in the skin, that they may "overwhelm" the skin and make it impossible for a pathologist to observe the changes that would be associated with, for example, primary seborrhea.

TREATMENT OF SEBORRHEA

In all cases of secondary seborrhea, the best treatment is obviously aimed at the primary underlying cause. However, adjunct symptomatic treatment of the seborrhea with topical shampoo products can hasten resolution. The aims of treatment are to (1) slow the epidermal turnover time towards normal (reduce the scaling at its source); (2) normalize the "oiliness" of the coat (decrease or supplement it, as necessary); (3) control seborrheic odor; and (4) remove excessive scaling and crusts from the coat. Consideration of these principles in relation to the patient will help you choose the ideal shampoo regimen.

The "classical" ingredients in antiseborrheic shampoos are now being supplanted, or in some cases replaced, by newer ingredients with purportedly (though not always conclusively proven) equivalent or better results. Generally, the actions of the major ingredients are as follows:

- **Tar:** Acts as an antimitotic to "poison" the epidermal cells and decrease their mitotic rate, thus stopping cell production at its source. Tar is also quite drying. It is slowly disappearing from shampoos, in part due to problems with standardization and in part due to (probably unfounded) concerns as to possible carcinogenicity.
- **Sulfur:** Also helps to normalize epidermal turnover time and the cornification process ("keratoplastic" action). Has some antipruritic, antimicrobial, and parasiticidal activity.
- **Salicylic Acid:** Helps to "break up" or dissolve the adherent scaling and crusting ("keratolytic" action), so it can be washed away by the detergent and water.
- **Benzoyl Peroxide:** Breaks up scaling and crusting but is very drying and can be irritating to some animals; excellent antibacterial activity; bleaches fabrics and haircoats!
- **Phytosphingosine:** A novel ingredient that is a component of the intercellular matrix of skin. It has antimicrobial, anti-inflammatory, and barrier-enhancing properties.
- **Antimicrobial Ingredients:** Most of the above ingredients have some antimicrobial action. In addition, some shampoos may contain specific compounds such as ketoconazole, chlorhexidine, piroxone, or others. These are aimed at reducing the count of the bacterial and/or yeast populations on seborrheic skin to reduce the incidence of secondary infections.
- **Humectant Ingredients:** Many antiseborrheic shampoos or post-shampoo sprays or rinses contain humectants, various oily or non-oily moisturizers to restore moisture to a dry coat.

The important general principles of antiseborrheic shampooing are to use the shampoos frequently (twice weekly at first), and to allow 10 to 15 minutes of contact time of the lather with the skin to allow for penetration.

The evidence for usefulness of fatty acid supplements ("coat conditioners" or supplementing diet with vegetable and animal fat) in canine seborrhea is thin. Some dermatologists recommend them, but it is generally uncommon for a fatty acid supplement alone to do much for seborrhea. It is, however, wise to insure that the pet is eating a high-quality diet and not being fed a marginally nutritious ration of table scraps or cheap dog food.

Primary seborrhea is a controllable, but not curable, disease. It is wisest to sit down with the client and explain the prognosis and the likely necessity of lifelong treatment. The mainstay of treatment for most dogs with primary seborrhea is topical therapy with antiseborrheic shampoos. Controlling secondary infections is always a consideration in these pets. Different patients tend either to get staphylococcus overgrowth, yeast overgrowth, or both, the same thing over and over again. Thus, it is important to identify which of these is a problem for the individual dog so that shampoo therapy can be tailored to the pet's needs.

Some dermatologists (including the author) believe that some dogs with primary seborrhea benefit from vitamin A supplementation of their diet. This disease is not a dietary deficiency, but vitamin A in high doses has pharmacologic actions including modification of the cornification process. The "right" dose has not been established, but a reasonable guideline is one 8,000 IU capsule (the common "standard" size in the US is 8,000 IU Vitamin A) per 5 kg of body weight per day.

Primary seborrhea is often accompanied by severe seborrheic otitis externa. The otitis starts as a ceruminous otitis, but if left alone often progresses to bacterial or yeast otitis, because the cerumen is "food" for the normal ear bacterial and yeast flora. Appropriate routine ear cleanings, using a cleaner that contains antimicrobial ingredient(s), are indicated to keep numbers of bacteria and yeast down. The owner should learn to clean the ears at home and do this routinely once weekly to every other week. If the otitis includes a substantial inflammatory component in the absence of infection, many pets will benefit by routine (1–2x weekly) use of a corticosteroid-only ear drop. Corticosteroids not only suppress inflammation, but also inhibit cerumen production. Some cocker spaniels with long-term inflammatory ear disease from any cause, including primary seborrhea, develop severe proliferative otitis. This can literally progress until the external ear canal is completely closed off and ossified. This makes treatment difficult to impossible. This is a preventable situation! Warn owners of seborrheic spaniels early on to avoid future problems!

Seborrhea is uncommon in cats, especially when compared with dogs. Principal causes to consider include a parasitism like lice, mites, or fleas. Allergic cats don't often get secondary seborrhea like dogs do. Primary seborrhea is not recognized in cats. Seborrhea appearing in a middle-aged to older cat, especially if moderate to severe, is a danger sign! It often indicates a potentially severe underlying metabolic disease, such as hyperthyroidism or diabetes mellitus. Always test for an internal medical problem in a seborrheic older cat!

Several unusual seborrheic syndromes exist, such as *granulomatous sebaceous adenitis* (GSA). This is an uncommon syndrome that can be seen in any breed, but is mostly reported in Viszlas, Akitas, Samoyeds, and Standard poodles of any age or sex. It is clearly a hereditary disease in Standard poodles. In this disease, the sebaceous glands appear to be destroyed by the dog's own inflammatory cells. The clinical signs are somewhat variable, but usually include a progressive, nonresponsive seborrhea with alopecia; there may be annular or circular areas of hair loss and scaling. This disease is diagnosed easily, but *only* by skin biopsy, and is a great example of why you should always do a skin biopsy in a severe seborrheic skin disease! Topical antiseborrheic shampoos and humectants are slightly helpful, but the prognosis is poor. Systemic cyclosporine A modified (5 mg/kg/day, orally) works well for many dogs with GSA, but is expensive.

Seborrhea is a complex, multifactorial disease, but consideration of the common pathogenetic features of the condition and careful diagnostic evaluation can lead to treatment strategies that will provide substantial lifelong benefit, even in primary seborrhea.

ON THE HORIZON: METHICILLIN-RESISTANT STAPHYLOCOCCI

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Coming soon to your town...the "flesh-eating bacteria" that no antibiotic will stop! News stories on emergence of resistance in staphylococci and other organisms are appearing in the public press with increasing frequency, sometimes with a rather alarming tone that prompts clients to question your therapeutic strategy more closely. What is really happening on this scene?

ALTERNATE STAPHYLOCOCCAL SPECIES

Our understanding over the past 30 years has always been that nearly 100% of cases of canine staphylococcal pyoderma are caused by the "canine strain" of staph, that is, *Staphylococcus intermedius*. Usually, staphylococcal organisms will stay on their "preferred host." *S. intermedius* is not transmitted to human beings under usual circumstances; human *S. intermedius* infections have mostly been limited to unusual situations and things like infected dog bite wounds.

Recently, increasing attention has been paid to the fact that the "human strain" of staph, *Staphylococcus aureus*, has been occasionally seen as a cause of canine infection. In this case, the organism probably was transmitted from the owner to the pet. Many human beings transiently or periodically harbor *S. aureus* in the nasal passages without clinical consequence. When we do see transmission, there is often "something odd" about the situation. For example, this may occur not as a garden-variety superficial staphylococcal pyoderma, but rather in something like purulent otitis media. Or, it may occur when there has been excessive use of multiple antibiotics, subtherapeutic dosing of antibiotics, or an immunocompromised host. It may be more common for a dog to become infected with *S. aureus* when one of the humans in the household is a healthcare worker.

The practical significance of canine *S. aureus* infections depends on the situation. Most strains of *S. aureus* are still quite susceptible to routine antibiotics such as the cephalosporins, and are easily treated, so this finding is of little consequence. However, if the household includes immunosuppressed individuals, or those who are to undergo surgery soon, the owner should be made aware of the fact that the pet may represent a "reservoir" of staph organisms that could be transmitted to these compromised family members, until the infection is fully treated.

Staphylococcus schleiferi is a newly identified coagulase-positive staphylococcus in dogs. The organism itself is not new, merely our recognition that this different type sometimes infects dogs. So far, there has been no strong or consistent association between *S. schleiferi* and disease severity, recurrence, or antibiotic susceptibility. At this point, there's not much practical significance to this finding.

Remember, also, that most laboratories do not report the species of *Staphylococcus* on a culture—they simply report "coagulase-positive staph," which means the organism could be any of these species, and so in practical terms, you may never know if you were indeed dealing with an *aureus*! Separating out the species involves extra time and expense, and is usually unnecessary, though you can order this procedure from the lab if you desire. This author believes it is prudent in any case where the organism appears methicillin-resistant (see discussion below) to order a staph speciation. The main reason is to detect the presence of a methicillin-resistant *S. aureus*, which is potentially a human health hazard.

EMERGENCE OF METHICILLIN-RESISTANT STAPHYLOCOCCI

There has been a recent increase in reports of multi-drug resistant staphylococcal strains. These strains include the *intermedius, aureus,* and *schleiferi* varieties. In particular, the methicillin-resistant staphylococci (MRS) are of concern.

Methicillin is a laboratory antibiotic, used to test general susceptibility of the bacterium to the "penicillinase-resistant penicillin" group of antibiotics. Clinically-used antibiotics in this group include oxacillin, dicloxacillin, and amoxicillin/clavulanic acid; methicillin itself is not used on patients. If the organism is methicillin-resistant in the laboratory, it will be *clinically resistant to all penicillins and cephalosporins*. These MRS are still uncommon in many areas of the US, but in some areas (notably the northeast urban areas) they may approach 30% of isolates obtained from dogs with pyoderma.

What is the significance of these organisms? First, if you treat a dog with staph pyoderma with a beta-lactam antibiotic (cephalosporin or penicillin) and there is no response, culture and susceptibility testing is now mandatory. Fortunately, most veterinary strains of MRS are still susceptible to routine antibiotics such as trimethoprim-sulfa, clindamycin, or a fluoroquinolone. If you have such a patient in your hospital, you need not have the dog under full isolation procedures, but you should isolate the patient to the extent you can, and minimize traffic from this patient to other dogs in the clinic, especially the surgery and critical care areas.

Second, if you do identify an MRS organism, especially if it appears to be very resistant, *you should order a staph speciation*. If the organism turns out to be a highly resistant methicillin-resistant, human-origin *Staphylococcus aureus* (MRSA), the owner should be notified of this fact so they can discuss the situation with their own health care provider. This patient is a potential human health hazard and should be considered so until the infection is fully treated.

Third, the emergence of MRS in the veterinary world suggests that we must redouble our efforts to use antibiotics wisely and judiciously, and reconsider all efforts to use alternate non-antibiotic treatments if possible in the face of recurrent infections.

DOGS THAT ITCH: DETERMINING THE CAUSE AND STOPPING THE FRENZY!

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Pruritus is one of the most common and frustrating aspects of canine dermatologic disease. Each of us is very familiar with the physical damage that constant scratching causes, but many dogs with chronic itch can also have personality changes that exacerbate the problem. And if they don't have personality changes, their owners surely do! Controlling itch is critical to successful management of canine dermatologic disease. The case of each client and pet should be approached individually, as there is great variation in how much itch each client and pet can tolerate. It is useful to determine the level of itch for each patient, as that determination will allow us to develop a short list of potential causes, which then enables us to develop a rational diagnostic and treatment plan. Most dogs with pruritic skin disease will have diseases that are manageable, not curable. And for most dogs, we can decrease itch but not ablate it. Acknowledging these facts ourselves and helping our clients accept these facts will allow us to have an impact on canine pruritus, one patient at a time.

Triaging dermatology patients requires a good grasp of the history for each dog. Taking a standardized history is very important. Because some owners are better oral historians than others, a dermatology history questionnaire is immensely helpful. If you have a clinic website, you can have these forms available on line and ask your clients to download and fill them out before they come; alternatively, the clients can fill them out while they wait to be seen. You can make this task easy by asking your client to circle or check appropriate responses. This format pleases the minimalist. I do recommend having spaces to write in extra stuff for those detail-oriented clients who like to be complete. These questions can easily fit on one side of a page, allowing you to scan it before your examination:

1. Does your dog itch/scratch/chew/lick/rub?
   Yes No
2. What parts of the body?
   Face Ears Neck Armpits Legs Feet
   Chest Back Belly Stomach/Groin Other
3. On a scale from 1 to 10, how itchy is your dog?
   1 2 3 4 5 6 7 8 9 10
4. Is your dog's itch seasonal or nonseasonal?
   Nonseasonal Seasonal
5. If you circled nonseasonal, are there times of the year when he/she is worse?
   Yes No
6. If you circled seasonal, in what season(s) does your dog itch?
   Spring Summer Fall Winter
7. At what age did your dog start itching?
8. What other pets do you have? Are they itchy?
9. What medications have you used? Which ones worked?
   List Medications Effective Not effective

The next step is a good dermatologic exam. This requires good light and magnification when necessary. I often use the little magnifier on the otoscope to look at lesions. Rolling the dog over and looking at the bottoms of the feet, as well as under the tail is important, as is riffling the coat to see the skin over the back. You will be looking for primary lesions, such as papules, pustules, macules, or nodules. You will also be looking for secondary lesions, such as excoriations, crusts, scale, and alopecia. Gentle otoscopy should also be performed to determine if the dog has an ear infection or whether the ear canals are merely red. During the exam, you can ask the owner which came first, the itch or the lesions. This information is useful as atopic dermatitis has often been termed "an itch that rashes" whereas a disease like scabies has primary lesions of papules which itch.

The next step will be to develop a list of differential diagnoses and a plan by which to sort them out. I usually tell the clients we will develop a short-term plan and a long-term plan to control the itch. The short-term diagnostic plan consists of skin scrapings and cytologies, and maybe a dermatophyte culture if the history and physical exam warrant it. If you live in a flea-ridden area, then using a flea comb as part of your examination is also a good addition to your dermatologic toolbox. Skin scrapings will help us determine if *Demodex* mites are present. If done properly, negative skin scrapings will rule out demodicosis in most cases. Negative skin scrapings NEVER rule out scabies or cheyletiellosis. Skin cytologies help characterize the microbial infections that are present: bacteria, yeast, or both. The short-term treatment plan will be to rule out scabies or cheyletiellosis if indicated, to control fleas if indicated, and to get rid of all microbial infections. Short-term steroid therapy is indicated if the dog is severely pruritic.

In one month, we meet with the patient and client again to determine how much itch has been resolved by treating ectoparasites and microbial infections. Then we develop the long-term plan to control residual itch. The long-term diagnostic plan might be to perform elimination diet testing to rule out food allergy or perform intradermal skin testing or serum allergy testing to discover those antigens contributing to atopic dermatitis/atopy. It will include the judicious use of corticosteroids, antihistamines, and possibly cyclosporine. Diagnostic tests such as bacterial culture and sensitivity or biopsy could be part of either the short term or long-term plan, depending on what the dog looks like during the first exam. Keep in mind that biopsy will not help you sort out the different types of allergic skin disease.

Table I contains a list of common skin diseases and quantification of the itch. Using this table, we will work through a series of patients with pruritic skin disease, discussing the key historical and clinical features, as well as the diagnostic plans, and the treatment plans for each. As a general plan, the following advice is helpful.

Table 1. A Partial List of Pruritic Skin Diseases of the Dog

Intensely Itchy 8–10/10	Moderately Itchy 4–7/10	Mildly Itchy 1–3/10	Variably Itchy 1–10/10
Sarcoptic Mange*	Early uncomplicated atopy	Dry skin	Cheyletiellosis
Food Allergy (some)*	Food allergy (most)	Pyoderma (some)	Demodicosis
Flea Allergy (most)*	Flea allergy (some)	Atopy (few)	Pemphigus foliaceus
Atopy (chronic and/or infected	Pyoderma (many)		Dermatophytosis
Malassezia dermatitis	Contact allergy		Mycosis fungoides
Pyoderma ("staphylococcal hypersensitivity") Staphylococcal colonization			
Acral pruritic nodule/lick granuloma			

* The three most itchy skin diseases

For itch, rule out ectoparasites, rule out infections, rule out food allergy, and then deal with what is left! Usually, what is left is atopy/atopic dermatitis, and these dogs are probably best referred for intradermal skin testing and immunotherapy. Atopic dogs will be high maintenance dogs for the rest of their lives, for both their owners and their veterinarians. The more unusual diseases associated with itch will look unusual; these are patients you will wish to biopsy for a diagnosis or refer for diagnosis and treatment recommendations.

PATIENT 1: MR. BIG, 3-MONTH- OLD MALE POODLE

- **Key historical features**: Young intensely itchy dog purchased at roadside stand
- **Key diagnostic features:** Erythematous papular rash, positive pinnal-pedal reflex, scale and crust on ears, positive cytologies for cocci/yeast, response to treatment (negative skin scrapings a red herring)
- **Treatment**: Topical selamectin every 2 weeks for 3 treatments, oral cefpodoxime and fluconazole, antiseborrheic shampoos (methylprednisolone for pruritus)
- **Final diagnosis:** Sarcoptic mange, with secondary pyoderma and *Malassezia* dermatitis
- **Important points**:
    - o Negative skin scrapings do not rule out sarcoptic mange.
    - o It is important to treat the bacterial and yeast infections associated with mange.
    - o Because *Sarcoptes* induces a hypersensitivity reaction, corticosteroids may be helpful in palliating the itch.

PATIENT 2: KOBY, 9- YEAR-OLD MALE MALAMUTE MIX

- **Key historical features**: Partial response to antibiotics, steroids (mild pruritus a red herring?)
- **Key diagnostic features**: Crusting on ear margins, positive pinnal-pedal reflex, skin scrapings positive for mites, cytology positive for cocci, low thyroid hormone levels
- **Treatment:** Oral ivermectin, oral cephalexin, antiseborrheic shampoos, thyroid supplementation
- **Final diagnosis**: Sarcoptic mange, hypothyroidism, secondary pyoderma
- **Important points**:
    - o Older dogs can get scabies.
    - o Although no other dogs in the house were itchy, they may have been asymptomatic carriers and possible sources of infection for our patient; all in-contact animals should be treated.
    - o Large numbers of mites may be present in debilitated dogs: "Norwegian scabies."
    - o An underlying metabolic disease may predispose to large numbers of mites; the depression associated with hypothyroidism may have made him less itchy with the disease.
    - o Prolonged treatment times may be required for dogs with large numbers of mites.

PATIENT 3: BONNIE, 3-YEAR-OLD FEMALE SPAYED WEST HIGHLAND WHITE TERRIER.

- **Key historical features:** Owners' observations of fleas, short-term response to steroids, insufficient flea control for patient and her housemates
- **Key diagnostic feature:** Presence of fleas on patient, pattern of alopecia, response to treatment
- **Treatment:** Oral Capstar and increased frequency of topical Advantage for patient, oral lufenuron and topical selamectin for cats, treatment of house and yard
- **Final diagnosis**: Flea allergy dermatitis
- **Important points:**
    - o Flea allergy dermatitis requires integrated pest management on all animals in the house.
    - o Sometimes itch control requires only increasing awareness of the flea life cycle and increasing vigor of flea control. Steroids not required for this dog.

PATIENT 4: INGRID, 3-YEAR-OLD FEMALE SPAYED SHEPHERD CROSS

- **Key historical features**: Pruritus at a young age, inappropriate dietary trials, variable response to steroids, no response to treatment for scabies
- **Key diagnostic features**: Failure to respond to treatment for scabies, cytologies positive for cocci and yeast, response to treatment for infections, eventual response to strict dietary trial and food challenges
- **Final diagnosis**: Food allergy, with secondary pyoderma and *Malassezia* dermatitis
- **Important points**:
  - Dietary trials must be complete. All edible treats and toys must be stopped.
  - Infection control can improve the comfort level of food allergic dogs.
  - Food challenges can enable the dog to go back on a commercial diet.
  - Not all food-allergic dogs are refractory to steroids.
  - It may be important to try more than one diet if food allergy is suspected highly.

PATIENT 5: SCHOTZE, 4-YEAR-OLD FEMALE SPAYED SHIH TZU

- **Key historical features**: Nonseasonal pruritus with seasonal flares, exacerbation following move to warmer climate
- **Key diagnostic features**: Skin cytology, response to flea control, response to dietary trial, intradermal skin testing
- **Final diagnosis:** Flea allergy dermatitis, food allergy, atopic dermatitis with secondary pyoderma and *Malassezia* dermatitis
- **Important points**:
  - Dogs can have multiple allergies.
  - Observing response to flea control and food trials requires that the infections be managed.
  - Controlling fleas and elimination diet testing revealed that atopic dermatitis was still a possibility, so skin testing and immunotherapy were pursued.

PATIENT 6: TESSIE BELLE, 1-YEAR-OLD FEMALE SPAYED WEST HIGHLAND WHITE TERRIER

- **Key historical features**: Moderate to severe pruritus with no response to treatment for scabies, breed and source of dog (relinquished to breed rescue society)
- **Key diagnostic features**: No response to treatment for scabies, skin cytologies positive for cocci and yeast, response to infection control, positive blood allergy test, positive intradermal skin test
- **Final diagnosis:** Flea allergy dermatitis and atopy with secondary pyoderma and *Malassezia* dermatitis
- **Important points:**
  - *Malassezia* is an intensely pruritic disorder.
  - *Malassezia* can be brought under control with topical therapy but requires daily bathing for several weeks.
  - Infection control can reduce itch dramatically in atopic dogs.

PATIENT 7: BOUDREAUX, 5-YEAR-OLD MALE CASTRATED LABRADOR CROSS

- **Key historical features:** Poor response to antibiotics, poor response to Depo Medrol, nonseasonal pruritus with waxing and waning nature
- **Key diagnostic features**: Distribution of primary lesions on face, ears, footpads, results of biopsy
- **Final diagnosis**: Pemphigus foliaceus with secondary bacterial pyoderma
- **Important points**:
  - Historical ringer was the seasonal nature of the disease; this dog's pemphigus flares every summer.
  - Primary lesions of pustules and crusted papules on face and ears very suggestive.
  - If skin disease looks strange, biopsy it!

PATIENT 8: CLANCY, 6-YEAR-OLD OLD MALE CASTRATED ENGLISH BULLDOG

- **Key historical features:** Atopic dog on immunotherapy well regulated for 3 years; relapsing prurritus and erythematous plaques, collarettes over last 6 months; poor response to antibiotics and steroids
- **Key diagnostic features:** Negative cytology, skin biopsy, distribution and character of lesions (if it is weird, biopsy it)
- **Final diagnosis**: Epitheliotropic T-cell lymphoma (mycosis fungoides)
- **Important points**:
  - Relapsing itch after years of good control on immunotherapy.
  - Poor response to antibiotics and steroids.
  - Unusual distribution, appearance, and feel of lesions.

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DIFFERENTIATING CANINE ALLERGIC SKIN DISEASES

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Pruritus is the predominant clinical sign of allergic skin disease. Pruritus is defined as a sensation that elicits the desire to scratch. Together with self-trauma, pruritus is the most common reason for a dog to be presented to a veterinary hospital. Pruritus may be manifested in the dog by licking, chewing, rubbing, hair removal, harassing of owners, irritability, and personality change (lack of tolerance, aggressive behavior). The concept of a *threshold phenomenon* is important in the understanding of pruritus. An individual may tolerate a certain pruritic load without provoking clinical signs but a small increase in that load may push that individual over the threshold initiating clinical signs of pruritus. While some mediators initiate the sensation of pruritus, others simply lower the threshold of pruritus. *"Summation of effect"* occurs whereby additive pruritic stimuli from different coexistent skin diseases may raise an animal above its individual pruritic threshold.

CANINE ALLERGIC SKIN DISEASES – FREQUENCY

Globally, the most common allergic canine skin diseases are, in frequency of occurrence, flea allergy dermatitis, atopic dermatitis, and food allergy (adverse reactions to food). Flea allergy dermatitis is not only the most common skin disease seen in small animal practice in most countries in the world; it is the most common disease of any organ system seen in small animal practice worldwide. Fleas parasitize animals in virtually every area on earth with the exception of locations above 1500 meters elevation and regions such as deserts with very low humidity. However, somewhat surprisingly, flea allergy dermatitis is commonly underdiagnosed all over the world. There are many reasons for this including sociocultural biases against having ectoparasites. The reported frequency of occurrence of different allergic skin diseases varies widely from study to study and is highly controversial. Many dermatologists have expressed the opinion that in parts of the world where fleas are common, flea allergy dermatitis comprises between 50% and 80% of allergic skin disease.

Recent data published by Jackson from a referral dermatology clinic at North Carolina State University offers data on the frequency of atopic dermatitis and food allergy in comparison to each other. However, their data on the frequency of flea allergy dermatitis, and flea allergy seen in conjunction with other allergic skin diseases seems surprisingly low. At UC Davis, our dermatology service sees flea allergy dermatitis as the most common allergic skin disease despite being a referral center.

Jackson and others looked at 91 dogs with allergic skin disease. Here are their results:

- 46% – Atopic dermatitis only
- 23% – Food allergy only
- 20% – Atopic dermatitis & food allergy
- 4% – Food allergy & flea allergy dermatitis
- 3% – Atopic dermatitis, food allergy, & flea allergy dermatitis
- 2% – Flea allergy dermatitis only (bias of a referral center?!)

One can thus extrapolate from these data that 66% have atopic dermatitis, 43% have food allergy, and 20%.of these dogs have both diseases.

DIFFERENTIATING ALLERGIC SKIN DISEASES BY SIGNALMENT PREDILECTIONS

Predilections vary between the three most common allergic skin diseases. Prioritize your index of suspicion based on differences in signalment, history, and physical findings (most common affected sites, lesions).

Breed Predilections

Flea allergy dermatitis can be seen in any breed, but it is more common in "allergic breeds." Atopic dermatitis is most common in the Golden Retriever, Labrador Retriever, Wirehaired Fox Terrier, Dalmatian, West Highland White Terrier, Weimaraner, other small Terriers, Irish Setters, Chinese Shar Pei, and in Spaniels. Food allergy (controversial) may be more common in Labrador Retrievers, Cocker Spaniels, Golden Retrievers, Soft-Coated Wheaten Terriers, Dalmatians, West Highland White Terriers, Collie Dogs, Chinese Shar-Peis, Lhasa Apsos, Springer Spaniels, Miniature Schnauzers, Dachshunds, Boxer Dogs, and German Shepherd Dogs.

Age Predilections

The age of onset varies between different allergic skin diseases. Flea allergy dermatitis can be seen in any age, but is more common in dogs over 6 months of age. The average age of onset of atopic dermatitis is between 1½ and 3 years of age, but it can occur in dogs as young as 6 months (rarely – younger!) and occurs rarely in dogs over 6 years of age. Food allergy is highly variable in onset and can begin from 4 months to 14 years; up to 50% may develop the disease at less than 1 year of age. Useful or reliable sex predilections have not been reported.

History Predilections

As far as speed of onset, flea allergy dermatitis usually is of rapid onset. In contrast, atopic dermatitis usually is insidious and gradual in onset. Food allergy usually is insidious and gradual in onset, but occasionally may be more rapid in onset.

Seasonality Predilections

Flea allergy dermatitis is contingent on flea availability, which depends on weather, seasonal temperature and humidity changes, and severity of winters. Atopic dermatitis is contingent on allergen availability, and commonly may begin seasonally (summer), but annually adds time spring & fall, and finally becomes year around. Food allergy should not be seasonal.

Physical Findings – Site Predilections

Flea allergy dermatitis affects predominantly the caudal half of the dog, and is bilaterally symmetric involving the dorsal lumbosacral, tailbase, perineum, medial and caudal thighs, and umbilical regions. Atopic dermatitis most commonly affects the face, paws, distal extremities, ears, ventrum, and caudal carpus. Food allergy affects the face, ears, extremities, paws, and ventrum (similar to atopic dermatitis).

Physical Findings – Lesions

Lesions of flea allergy dermatitis include crusted papules, erythema, and excoriations. Chronic changes are lichenification, hyperpigmentation, alopecia, fibropruritic nodules, and secondary infection. Atopic dermatitis initiates self-trauma leading to erythema, alopecia, excoriation, and the chronic changes of lichenification and hyperpigmentation, and secondary infections. Few "primary" lesions are seen. Food allergy initiates self-trauma leading to erythema, alopecia, and excoriation. Chronic changes include lichenification and hyperpigmentation, and secondary infections. Few "primary" lesions are seen, similar to atopic dermatitis.

DIFFERENTIATING ALLERGIC SKIN DISEASE BY RULING OUT FLEA ALLERGY AND FOOD ALLERGY

There are no laboratory tests available that consistently can rule in or out allergic skin disease in the dog. Therefore, since flea allergy dermatitis is the most common allergic skin disease, it is logical to rule out flea allergy by several months of strict flea control. If pruritus remains after strict flea control, initiate a strict elimination diet to rule out food allergy.

Ruling Out Flea Allergy Dermatitis

One must convince the owner that flea allergy may be the correct diagnosis. In order to accomplish this, one must defuse cultural bias, explain why fleas are not seen, and explain that flea allergy is the most common disease on the planet. Then, show defects in current or past flea control. These defects include not treating all animals, not treating in-and-out cats, lack of consistency, and substitution of over-the-counter products, and extreme environmental issues. Institute modern flea control for 6 to 8 weeks ("Prove me wrong!").

Ruling Out Food Allergy

Convince the owner that an elimination diet must be incredibly strict. Then show defects in past attempted elimination diets (snacks, food with medicine, flavored heartworm preventatives, IDIs, or other medications, and flavored toothpaste). Institute a strict elimination diet for 8–12 weeks. If there is improvement, continue the diet. Do not accept food allergy as the diagnosis without rechallenge with the original diet! When rechallenging with the initial food, do not change anything else in the treatment regimen (antibiotics, anti-yeast medications, flea control, antihistamines, and topical therapy).

Ruling in Atopic Dermatitis

Canine atopic dermatitis is a diagnosis of exclusion. "Allergy testing" (either intradermal testing or allergen-specific IgE serology) are performed *only* in animals that meet the clinical criteria of atopic dermatitis and where other pruritic skin disease that can be more readily diagnosed definitively have been ruled out. Testing is *only* performed to select antigens in animals where the decision already has been made to embark on the lifetime pathway of allergen specific immunotherapy.

MANAGEMENT OF CONCURRENT SKIN DISEASES

Allergic skin diseases commonly coexist. One must manage **all** allergic skin diseases present to be successful, thus reducing the animal below pruritic threshold. Concurrent confirmed or suspected flea allergy dermatitis must be managed. Concurrent secondary pyoderma or bacterial overgrowth and *Malassezia* dermatitis also must be managed.

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CANINE AND FELINE DEMODICOSIS: WHERE ARE WE NOW?

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CANINE DEMODICOSIS

Canine demodicosis is a common noncontagious parasitic skin disease caused by an overpopulation of the host-specific follicular mites of the genus *Demodex*. Most cases of canine demodicosis are caused by *Demodex canis*, although two other species of demodicid mites are reported. Localized demodicosis is a common mild and benign self-limiting disease. In contrast, generalized demodicosis is a serious and potentially life-threatening disease. Most cases of generalized demodicosis are juvenile in onset and develop in dogs less than 1 year of age.

A genetically preprogrammed immunologic defect probably is responsible for the juvenile-onset, generalized demodicosis. Immunosuppressive diseases (hyperglucocorticoidism, iatrogenic hyperglucocorticoidism, lymphoid neoplasia, leishmaniasis, and hypothyroidism) can induce adult-onset demodicosis. Marked breed predilections and clustering in litters support a hereditary basis for juvenile-onset generalized demodicosis. Data suggests an autosomal recessive mode of inheritance. The American Academy of Veterinary Dermatology (AAVD) adopted a resolution in 1981 sponsored by Dr. Robert Kirk recommending "neutering all dogs who have had generalized demodicosis so that the incidence of the disease is decreased and not perpetuated."

Generalized canine demodicosis is characterized by the progression of multifocal, erythematous, partially alopecic, crusted macules that eventuate in plaques. Boggy, crusted plaques, alopecia, and exfoliation are signs of more severe disease. Hyperpigmentation, lichenification, and scarring develop with chronic infection. Secondary bacterial infection with generalized deep folliculitis and furunculosis, occasional cellulitis, and tissue devitalization may contribute greatly to disease severity, morbidity, and mortality. Hair loss may be surprisingly minimal in long-coated breeds with long anagen hair cycles such as the Maltese, Shih Tzu, Lhasa Apso, and Miniature Poodle; this may lead to a decreased suspicion for demodicosis.

Diagnosis

Diagnosis is not difficult in most dogs with demodicosis. Skin scrapings or hair plucking readily demonstrate mites. A medium grade of mineral oil is used for skin scrapings. Micro-spatulas (Fisher Scientific catalog #21-401-20) are excellent tools for performing skin scrapings. Hair plucks are a less sensitive, but gentler method of obtaining mites. The author uses hair plucks predominantly in areas such as the periorbital region where performing a skin scraping may be difficult. Recently, impression smears of exudative lesions have been shown to be an additionally useful method of diagnosing demodicosis. Skin biopsy may be required to rule out demodicosis if the disease is chronic, severely affects the feet, or in the Chinese Shar Pei.

Treatment

Treatment of **canine generalized demodicosis** remains challenging. There is no treatment for generalized demodicosis that is 100% effective, even though multiple options currently are available. However, most dogs can be successfully managed long-term. Corticosteroid usage must be avoided.

Secondary deep pyoderma usually coexists with canine generalized demodicosis and must be treated aggressively. Antibiotics such as cephalexin, enrofloxacin, marbofloxacin, and clavulanic acid-potentiated amoxicillin are used most commonly and usually are continued for a minimum of 8 weeks.

Topical adjunctive therapy is beneficial. Antibacterial and follicular flushing shampoos containing benzoyl peroxide aid greatly in management of both demodicosis and secondary pyoderma. Whirlpool baths using chlorhexidine remove debris and encourage drainage in severely affected dogs.

Amitraz (Mitaban®, Pfizer Animal Health) remains the only FDA-approved treatment for generalized canine demodicosis. Before amitraz rinses, all medium- and long-coated dogs should be clipped and the hair kept short throughout therapy. Clipping plus benzoyl peroxide–containing shampoos afford better penetration of the dipping solution. Mitaban is diluted according to label directions in the US (0.025% solution) and applied every 2 weeks. A stronger amitraz solution (0.050% solution) has been used on a weekly basis routinely in Germany, Australia, and elsewhere. Using evidence-based medicine, good evidence is available for the efficacy of amitraz rinses (0.025%–0.05% solutions) used every 1 or 2 weeks.

Amitraz rinsing should be performed either outdoors or in an open garage. Rubber gloves should be worn by the applier. Amitraz is an MAO inhibitor and should not be used by anyone taking other MAO-inhibiting drugs. Continuous rinsing of the entire dog with the dipping solution and soaking of the feet in the solution should continue for 15 minutes. The dog should be kept as dry as possible (avoiding of walking on wet lawns) between rinses.

Amitraz rinses should be continued every 2 weeks until multiple negative skin scrapings and hair plucks (no adults, larvae, or eggs) are achieved. After negative scrapings and hair plucks have been achieved, three additional rinses should be performed. After three additional rinses, reexamination should include 6 to 10 skin scrapings and hair plucks before rinses are terminated. It is not uncommon for 10 to 15 rinses to be required before negative scrapings are achieved.

Side effects of amitraz therapy include lethargy, weakness, ataxia, hyperglycemia, polyuria, hypothermia, and bradycardia. Atipamezole (Antisedan®, Pfizer Animal Health)(50 μg/kg, IM) and yohimbine (0.11 mg/kg, IV; 0.25 mg/kg, IM) may be used as a pretreatment in dogs with previous reactions to amitraz or can be used as antidotes for toxicity.

Resistant cases may require off label application of amitraz rinses weekly rather than biweekly. In cases that are controlled but not cured, a maintenance program of rinses every 1 to 2 weeks may be instituted to keep mite numbers low and clinical signs minimized. Dogs with adult-onset demodicosis and concurrent immunosuppressive diseases frequently require extended therapy regimens.

Ivermectin (Ivomec®, Merial) is a commonly used, but unapproved, treatment for generalized canine demodicosis. Many of the dogs referred to the University of California have failed amitraz therapy. These dogs are treated with ivermectin given daily per os at a dosage between 400 and 600 µg/kg daily. High-dose ivermectin is the most efficacious and cost-effective treatment for generalized demodicosis that is nonresponsive to amitraz. Using evidence-based medicine, good evidence is available for the efficacy of ivermectin given per os (300–600 µg/kg daily).

Severe adverse reactions to ivermectin have been reported in both dogs and cats. Collies are particularly sensitive with over 75% of Collies being either carriers or homozygous for the dangerous mutant MDR1 allele leading to neurotoxicity. Information on testing for this mutation can be found at http://www.vetmed.wsu.edu/depts-vcpl/ Other herding breeds such as the Shetland Sheepdog, Australian Shepherd, and Border Collie also may be at increased risk for toxicity. However, idiosyncratic toxicity may be seen in any breed.

Similar to the monitoring of efficacy used with amitraz topical therapy, dogs are reevaluated monthly until multiple negative skin scrapings and hair plucks (no adults, larvae, or eggs) are achieved. After negative scrapings and hair plucks have been achieved, therapy is continued for an additional 2 months. Two months beyond the last negative skin scraping and hair pluck, reexamination should include 6 to 10 skin scrapings and hair plucks before therapy is terminated. It is not uncommon for 4 to 6 months of therapy to be required before negative scrapings are achieved.

Milbemycin oxime (Interceptor®, Novartis) is another commonly used, but unapproved, treatment for generalized canine demodicosis. It is used less frequently than ivermectin as milbemycin therapy is considerably more expensive. However, milbemycin is the safest avermectin used for the treatment of demodicosis. In dogs that have failed amitraz therapy, milbemycin oxime is the treatment of choice for generalized demodicosis in herding breeds such as the Collie. Milbemycin also is recommended for small dogs based on cost. Milbemycin is given daily per os at a dosage of 2 mg/kg daily. Using evidence-based medicine, good evidence is available for the efficacy of milbemycin given per os (2 mg/kg daily).

Milbemycin therapy is considerably less toxic than ivermectin therapy. Side effects are rare, but at high dosages may include vomiting, stupor, trembling, and ataxia.

Identical to the monitoring of efficacy used with ivermectin oral therapy, dogs are reevaluated monthly until multiple negative skin scrapings and hair plucks (no adults, larvae, or eggs) are achieved. After negative scrapings and hair plucks have been achieved, therapy is continued for an additional 2 months. Two months beyond the last negative skin scraping and hair pluck, reexamination should include 6 to 10 skin scrapings and hair plucks before therapy is terminated. It is not uncommon for 4 to 6 months of therapy to be required before negative scrapings are achieved.

Moxidectin (ProHeart® 6, Fort Dodge Animal Health), currently not available in the US, also has been used as another unapproved, treatment for generalized canine demodicosis. Evidence-based medicine indicates good evidence for the efficacy of moxidectin given per os (400 µg/kg daily).

FELINE DEMODICOSIS

Feline demodicosis is a rare or regional skin disease caused by at least three different species of demodectic mites. Feline superficial demodicosis is a contagious, transmissible frequently pruritic generalized skin disease caused by the surface-dwelling *Demodex gatoi*. Feline follicular demodicosis caused by the feline follicular mite, *Demodex cati* resembles *Demodex canis* infection in dogs.

Feline superficial demodicosis does not have a canine counterpart. It is believed to be rare in most of North America, but is found more commonly in localized enzootic regions of the southern and southeastern US. Feline superficial demodicosis may be increasing in frequency where modern insect-specific parasiticides that do not kill acarids are used for flea control. Clinical features vary from asymptomatic alopecia to alopecia with variable pruritus and self-trauma. If pruritus is absent, cats can present with diffuse, bilaterally symmetric alopecia, plus or minus scaling, affecting the ventral and lateral trunk and caudal legs. Pruritus, if present, usually is intense leading to erythema, crusting, and excoriation. Skin scrapings may not yield mites or eggs in pruritic cats since excessive grooming can remove surface-living mites. Skin scrapings of non-pruritic cats may yield large numbers of mites.

Feline follicular demodicosis due to *D. cati* is rare and may present as either localized or generalized follicular demodicosis. Similar to canine localized demodicosis, feline localized demodicosis is a mild and self-limiting disease. Similar to canine generalized demodicosis, feline generalized follicular demodicosis due to *D. cati* and seems to require diminished immune response. Immunosuppressive diseases such as feline immunodeficiency virus infection (FIV), feline leukemia virus (FeLV), diabetes mellitus, hyperglucocorticoidism, and neoplasia may initiate feline generalized follicular demodicosis.

Feline generalized follicular demodicosis is a less severe disease than canine generalized demodicosis. Predominantly asymptomatic and subtle erythema with variable alopecia, scaling, and crusting may be seen. Lesions most commonly affect the face, neck, trunk, or extremities. Systemic signs referable to underlying immunosuppressive systemic diseases may be noted.

Treatment

For the treatment of feline demodicosis, there is good evidence-based information to recommend lime sulfur rinses (LymDyp®, DVM Pharmaceuticals) (2%) weekly. There is fair evidence to support the use of amitraz rinses (0.0125%) weekly. (See additional information above under the treatment of canine generalized demodicosis.)

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NEWLY DESCRIBED BREED-BASED SKIN DISEASES

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Signalment (age, breed, sex) predilections are becoming much more important in all branches of clinical medicine as more epidemiologic data are accrued. Breed predilections are seen as a feature of many skin diseases of the dog and cat. These breed predilections can aid diagnosis via prioritizing differential diagnosis based on likelihood of occurrence in that breed. Some diseases have such striking breed predilections that it may greatly facilitate diagnosis. Diseases with strong breed predilections are likely to have an inherited basis.

Since the year 2000, multiple new breed-based skin diseases have been reported in dogs and cats. Three "new" skin diseases affecting the planum nasale and philtrum of dogs and cats have been diagnosed. All three diseases have marked breed predilections. Another disease seen in Persian and Himalayan cats has been noted occasionally by dermatologists for many years but was not described until 2000. The first report of proliferative necrotizing otitis of kittens was published in 2005 in a textbook.

NASAL PARAKERATOSIS OF LABRADOR RETRIEVERS

Nasal parakeratosis of Labrador retrievers is a rare syndrome characterized by proliferative changes of the planum nasale. Autosomal recessive inheritance is hypothesized. Clinical features included dry, rough, proliferative keratinous adherent debris forms on the planum nasale. Lesions are most severe dorsally. The planum may change color from black to gray or brown. Owners have noted that the affected planum becomes paler after the surface is wet. Deep fissuring can initiate secondary infection. Affected dogs are otherwise healthy. In early stages, the process does not ablate the normal cobblestone appearance. Later, the process may ablate the normal architecture. This syndrome is seen exclusively in Labrador retrievers or their related crossbreeds. Black, yellow, and chocolate Labrador retrievers have been reported. Lesions develop between 6 months and 1 year of age and 13 of 18 affected dogs were males. The disease is visually distinctive. Possible differential diagnoses include nasodigital hyperkeratosis, zinc-responsive skin dermatosis, discoid lupus erythematosus, and pemphigus foliaceus.

There is no cure for this genodermatosis. Topical petroleum jelly or topical propylene glycol in water have been used with palliative success. Topical therapy must be continued long-term.

PROLIFERATIVE ARTERITIS OF THE NASAL PHILTRUM (SAINT BERNARDS)

Proliferative arteritis of the nasal philtrum is a rare and distinctive vascular disease affecting the nasal philtrum. The etiology is not known. An inherited disorder is strongly suspected as 4 of 5 dogs reported were Saint Bernards and 3 of 4 were closely related. The disease is characterized clinically by solitary, well-demarcated linear ulcers with adherent hemopurulent crusts affecting the nasal philtrum. Ulcers ranged in size from 3 to 5 cm in length, 2 to 15 mm in width, and 2 to 5 mm in depth. Arterial hemorrhage of variable severity occurred in all dogs. Affected dogs are otherwise healthy.

Progression is unclear. Affected dogs have experienced long-term problems with periodic more severe ulcerations. Four of 5 dogs were Saint Bernards and the fifth dog reported was a Giant Schnauzer. The syndrome is tardive in onset and affects adult dogs between 3 and 6 years of age. The disease is visually distinctive. Immediate surgical intervention is required if severe arterial bleeding is noted. Oral anti-inflammatory dosages of corticosteroids, topical corticosteroids, tetracycline and niacinamide, and omega-3 (fish oil) fatty acids have been palliative in some dogs. Treatment must be continued long-term.

ULCERATIVE PLANUM NASALE OF THE BENGAL CAT

Ulcerative planum nasale of the Bengal cat is a rare and distinctive skin disease characterized by fissures, crusts, and ulcers of the planum nasale reported only in Bengal cats. A defect resulting in high epidermal turnover and reduced thickness of the stratum corneum was hypothesized. An inherited disorder is strongly suspected as all affected cats have been Bengal cats. The disease has been seen in Sweden, Italy, the United Kingdom, and in the US (two cases in Northern California). Clinical features include scaling progressing to adherent crusting overlying erosions and ulcers. Pruritus or pain were not noted. Bleeding can occur. The disease is gradual in onset in Bengal cat kittens or young adults. Age of onset was between 4 months and 1 year of age. The disease is visually distinctive. Oral prednisolone and topical salicylic acid were palliative in some cats. Topical tacrolimus (Protopic^{R}) was very effective in a small number of cats. Lesions in some cats may resolve spontaneously.

FACIAL DERMATITIS OF PERSIAN AND HIMALAYAN CATS

Facial dermatitis is an uncommon and progressive, idiopathic facial inflammatory skin disease reported in young Persian and Himalayan cats. It is presumed to be inherited.

Tightly adherent, darkly colored, greasy or waxy debris mats the facial hair. Erythema and exudation occur as the syndrome becomes chronic. Lesions usually are more severe in the facial folds, but also are present in non-intertriginous locations. A bilaterally symmetric ceruminous otitis externa was seen in about half of the Persian cats seen by Bond. The muzzle, periorbital regions, and chin are affected. Less severe lesions may affect body regions beyond the head. Secondary pyoderma or secondary *Malassezia* dermatitis may increase severity of clinical signs.

Pruritus commonly becomes intense with chronicity. Submandibular lymphadenopathy may be noted.

Affected Persian cats first present between 10 months and 6 years of age. Males may be slightly over-represented. In addition to published reports, multiple other Persian and Himalayan cats have been seen by various dermatologists worldwide.

Facial dermatitis of Persian and Himalayan cats is visually distinctive. Clinical differential diagnoses are few. Adherent dark facial debris may be seen with severe feline acne. A primary seborrhea of Persian cats has been reported, but other body regions beyond the face frequently are affected.

PROLIFERATIVE NECROTIZING OTITIS OF KITTENS

(I am cheating a bit with this last disease; most cases have been seen in domestic shorthaired cats.) Proliferative necrotizing otitis of kittens is a rare, highly characteristic syndrome of unknown etiology. The syndrome is seen only in cats less than one year of age. An immunologic basis is suspected since the syndrome bears some resemblance histopathologically to hyperkeratotic erythema multiforme. At this time, there is no evidence to link this syndrome to infectious viral diseases. Polymerase chain reaction (PCR) testing for feline herpesvirus 1 has been negative in a small number of cats. Papillomavirus immunohistochemistry also has been negative.

Erythematous, well-demarcated plaques with adherent, thick keratinous debris develop on the medial aspect of the pinnae, the entrance to the auditory canal, and in some cats, the preauricular region of the face. Lesions develop rapidly and coalesce creating annular or serpiginous borders. Adherent crusts cover the lesions and become trapped in the hair coat. Erosion and ulceration occur as the syndrome progresses. The syndrome usually is asymptomatic. Mild pruritus or discomfort is noted when ulceration is present.

Lesions develop in kittens between 2 months and 6 months of age and regress spontaneously between 1 and 2 years of age. Most cases have occurred in Domestic Shorthaired Cats. Proliferative necrotizing otitis of kittens is visually distinctive. Diagnosis is confirmed by skin biopsy.

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ECTOPARASITICIDAL THERAPY

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FLEAS AND FLEA ALLERGY DERMATITIS

Flea allergy dermatitis is the most common skin disease seen in small animal practice in most countries in the world. Fleas parasitize animals in virtually every area on earth with the exception of locations above 1500 meters elevation and regions such as deserts with very low humidity. The cat flea, *Ctenocephalides felis,* is the primary flea species associated with flea infestation and flea allergy dermatitis in both dogs and cats. The average cat flea life cycle involving development through egg, larvae, pupa, and cocoon, and the adult takes between 3 and 4 weeks. However, the life cycle can be as short as 12 days or as long as 140 days. Adult cat fleas are obligate permanent ectoparasites, attracted to the host by warmth, movement, changes in light intensity, and respiratory carbon dioxide.

Advances in understanding flea biology and new methodologies available to combat multiple life stages of the flea have revolutionized our ability to deal with this disease. It is crucial to remember that the adult cat flea is an obligate parasite. However, since the bulk of the flea lifecycle (eggs, larvae, and pupa) occurs in the environment, environmental issues must always be addressed. Historically, flea control has required vigorously treating both the animal and the environment with a combination of insecticides and, more recently, insect growth regulators. Today, either topical or systemic anti-flea therapy may be the only management required. The new agents that have created this paradigm shift include imidacloprid, fipronil, selamectin, nitenpyram, lufenuron, methoprene, and pyriproxifen.

Skin disease associated with fleas is a complex hypersensitivity involving at least four immunologic processes: immediate hypersensitivity, late-onset immediate hypersensitivity, delayed hypersensitivity, and cutaneous basophil hypersensitivity. Blood consumption by female fleas averages 13.6 µL/day (75 female cat fleas can consume 1 mL/day). The majority of blood is passed out as partially digested feces to feed flea larvae.

The management of flea allergy dermatitis requires the prevention of flea bites plus the disruption of the life cycle of the flea. New products that have become available over the past 15 years have exponentially increased our ability to initiate flea control and manage flea allergy dermatitis.

Modern Flea Control

New, considerably less toxic prescription products that also are much easier to use are available that kill adult fleas and disrupt the flea life-cycle. Most insecticides can effectively kill fleas; preventing reinfestation is the problem. Ensuring long-term pet owner compliance is required for ongoing flea control. The comparatively recent development of both insecticides and insect growth regulators with novel and convenient dosage forms (such as spot-ons, collars, and oral products) coupled with prolonged residual activity has dramatically improved pet owner compliance and hence prevented reinfestations. Although insecticidal resistance most often is suspected when flea control measures have failed, lack of control more often results from lack of understanding of flea biology, poor application technique, or too infrequent reapplication of the products.

The goals of flea control should be elimination of existing fleas on affected animals, continued elimination of fleas acquired from infested premises, and the prevention of reinfestation. In order to accomplish these goals, an integrated flea control plan must be instituted. Effective residual adulticides must be used to kill fleas and provide residual killing activity and insect growth regulators should be used to used to disrupt flea reproduction. In addition, mechanical control procedures such as cleaning the pet's blankets, beds, pet carriers, and throw rugs and vacuuming or removing furniture that can house pre-adult fleas must be instituted. Prevention of pests that can carry fleas (rats, opossums, squirrels, raccoons, skunks, feral cats) from entering crawl spaces, foundation vents, porches, and garages also is important.

Modern Flea Control Products

New spot-on prescription products display superior efficacy, safety, and residual activity. These products need to be applied directly to the skin, not to the haircoat. Our strong clinical impression at UC Davis is that dogs and cats with severe flea hypersensitivity experience much better efficacy with these products applied every 3 weeks rather than monthly. Our clinical impression remains that either bathing or swimming degrades the efficacy of all of these products. Over-the-counter (OTC) competing products commonly are advertised as "just as good as what you can get from your veterinarian" plus "less expensive." In general, these products contain concentrated permethrin or other synthetic pyrethroids. All indications are that these OTC products do not have either the efficacy, residual activity, or the safety profile of the spot-on prescription products. Figure 1 summarizes the opinions of the author.

Personal Recommendations

Flea control must be regionalized and often personalized based on severity of possible infestation in your locale, number of dogs and cats in the environment, indoor/outdoor status, infested pests and strays in the environment, finances of the owner, and severity of disease versus magnitude of the infestation. The "average" dog or cat will respond to fipronil and S-methoprene, imidacloprid with or without lufenuron, or selamectin as sole therapy. Severely flea-allergic dogs will require fipronil and S-methoprene or imidacloprid plus permethrin, plus nitenpyram, with or without lufenuron. Severely flea-allergic cats will require spot-on preparations plus nitenpyram with or without lufenuron. Pump-sprays also may be beneficial as an adjunct.

TICKS

Tick infestation and tick bite hypersensitivity are highly variable regional skin diseases. In some parts of North

America, ticks are a major problem, while they are comparatively rare in many other areas. Ticks cause morbidity either by direct irritation from their bites, initiate hypersensitivity, or act as vectors for multiple bacterial, viral, rickettsial, or protozoal diseases. The author's comments on these products are presented in Figure 2.

Personal Recommendations

Tick control must be regionalized and personalized based on severity of possible infestation in your locale, number of dogs, indoor/outdoor/run free status, infested pests and strays in the environment, finances of the owner, and severity of disease vs. magnitude of infestation. 'The average dog' will respond to fipronil and S-methoprene, imidacloprid and permethrin, selamectin, or an amitraz collar as sole therapy. Severely affected dogs benefit from the combination of a spot-on product (fipronil and S-methoprene, imidacloprid and permethrin, or selamectin) plus an amitraz collar.

ACARIASIS – SARCOPTIC ACARIASIS, NOTOEDRIC ACARIASIS, CHEYLETIELLOSIS

Canine sarcoptic acariasis or "scabies" is an intensely pruritic, highly contagious, transmissible canine dermatoses caused by the epidermal mite *Sarcoptes scabei var. canis*. Transmission is usually by direct contact with an infested dog. Evidence supports clinical disease being a multifactorial hypersensitivity reaction. Sarcoptic acariasis may be increasing in prevalence with the advent and increased popularity of newer insect-specific flea control products. Formerly, we may have stopped scabies infestation when we were simply attempting to kill fleas. The author's comments on available products are provided in Figure 3.

Notoedric acariasis or feline scabies is a rare contagious mite infestation caused by the sarcoptid mite *Notoedres cati* characterized by crusting with extreme pruritus. The disease is rare in most parts of the United States, but may be found in localized endemic areas. Similar to sarcoptic acariasis, notoedric acariasis may be increasing in prevalence. *Notoedres* is highly contagious in cats and occasionally, may affect dogs or humans.

Cheyletiellosis is a contagious mite infestation seen in domestic animals, wildlife, and humans characterized primarily by scaling and crusting caused by different, but similar, species of *Cheyletiella* mites. Pruritus is variable. It may be seen more commonly in areas of the world where concerted flea therapy is not necessary or not consistent. *Cheyletiella* dermatitis may be increasing in prevalence on a wider basis with the advent of newer insect-specific flea control products. Infestations have been reported in dogs, cats, rabbits, squirrels, poultry, foxes, and humans. This disease may not be as uncommon as previously thought, since veterinarians may have a low index of suspicion. **Cheyletiella** mites may live in the environment for extended periods of time.

Modern Contagious Acarid Control Products

It is beneficial for the management of all three acarid infestations to isolate the affected animal(s) and clean the premises, and dispose of the animal's bedding or thoroughly cleanse it. For the management of canine sarcoptic acariasis, all dogs on the premises and any other dogs with significant contact with the affected dog should be treated. For the management of feline notoedric acariasis, all cats on the premises and any other cats with significant contact with the affected cat should be treated. The treatment of in-contact cats in households with canine sarcoptic acariasis and the treatment of in-contact dogs in households with feline notoedric acariasis are more controversial. If skin disease is present or if initial species-restricted therapy is ineffectual, treatment of the other species should be considered. All dogs and cats on the premises and any other dogs or cats with significant contact with the affected animal should be treated when cheyletiellosis is diagnosed.

The traditional approach of using weekly keratolytic shampoos followed by parasiticidal dips has been superseded by newer less labor-intensive methods of therapy. Lime sulfur (LymDip®, DVM Pharmaceuticals, Lime Plus Pet Dip®, DermaPet) is still used in circumstances where safety is an issue, especially in very young animals. Systemic corticosteroids may be used adjunctively to control pruritus during the first week of therapy. Paradoxically, pruritus may actually increase during initial therapy perhaps due to increased antigenic load. The comments of the author on these products are presented in Figure 3.

Personal Recommendations

It is important to maintain an index of suspicion for all three acarid infestations as a cause of skin disease in dogs and cats. Cheyletiellosis may present as exfoliation with minimal pruritus. All three contagious mite infestations may be increasing in frequency of occurrence. Most dogs and cats with mite infestations will respond to selamectin, ivermectin, or milbemycin. Based on approval for use on dogs and cats for mite infestations, selamectin is the drug of choice for all three mite infestations. If financial constraints preclude usage, ivermectin or milbemycin can be used as alternatives.

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Figure 1. Modern Flea Control Products

Imidacloprid (Advantage®, Bayer; Canada – Imidacloprid & Moxidectin - Advantage Multi®, Bayer; Europe – Advocate®, Bayer)
Advantages – larvicidal on the animal and kills/debilitates adult fleas on contact, ease of application
Disadvantages – does not have repellent action, diminished efficacy after bathing or swimming, does not have activity against ticks, occasional application site reactions
Bottom-line – Good narrow-spectrum product for fleas

Fipronil & S-Methoprene (Frontline® Plus, Merial), Fipronil (Frontline® Spray, Merial)
Advantages – Kills adult fleas, disrupts flea life cycle, ease of application, kills ticks, spray: rapid dispersion/coverage
Disadvantages – Does not have repellent action, some diminished efficacy after bathing or swimming, occasional application site reactions, spray is labor-intensive
Bottom-line – Good broader spectrum product

Imidacloprid & 44% permethrin (Advantix®, Bayer)
Advantages – Larvicidal on the animal and kills/debilitates adult fleas on contact, interrupts flea life cycle, repellant 'flushing' activity of permethrin, ease of application, also kills ticks and mosquitoes
Disadvantages – Dog-only product, do not use on cats, diminished efficacy after bathing or swimming, occasional application site reactions?
Bottom-line – Good broader spectrum product, dog only product

Selamectin (Revolution® [USA]; Stronghold® [Europe], Pfizer)
Advantages – Broad spectrum against many internal and external parasites, kills adult fleas plus larvae and eggs, kills ticks, kills many contagious ectoparasitic mites (*Sarcoptes, Notoedres, Cheyletiella, Otodectes*), ease of application
Disadvantages – Does not have repellent action, diminished efficacy after bathing or swimming, slower efficacy?, application site reactions?
Bottom-line – Good broader spectrum product

Nitenpyram (Capstar™, Novartis)
Advantages – Very rapid response with visual results, kills 100% of adult fleas within 6 hours, short-acting, ease of oral administration, give every 24–72 hours (half-life in dogs is 2.8 hours, half-life in cats is 7.7 hours) very safe product, adverse reactions not seen yet
Disadvantages – Does not have repellent action, does not disrupt flea life cycle, short-acting, does not have activity against ticks
Bottom-line – Good narrow spectrum product, use with spot-ons initially for rapid response, not for use as sole therapy, use in dogs requiring frequent shampooing, compliance problems?

Lufenuron (Program®, Novartis; Sentinel® [lufeneron + milbemycin oxime])
Advantages – Oral product, very safe product without known mammalian toxicity, adverse reactions not seen yet
Disadvantages – Does not kill adult fleas or pupa, time lag – 60–90 days required to disrupt flea life cycle, does not have repellent action, adult flea must feed on animal to ingest, does not have activity against ticks, must give with food
Bottom-line – Use with spot-ons for long-term control, not for use as sole therapy unless very closed environment, treat all animals, use in dogs requiring frequent shampooing, compliance problems?

Imidacloprid & Moxidectin – (Advantage Multi®, Bayer; Europe – Advocate®, Bayer)
Advantages – Broad spectrum against many internal and external parasites, larvicidal on the animal and kills/debilitates adult fleas on contact, ease of application, ear mites, sarcoptic acariasis?
Disadvantages – Does not have repellent action, diminished efficacy after bathing or swimming, does not have activity against ticks, application site reactions.
Bottom-line – Good broader spectrum product

Pyriproxifen (Nylar®) containing collars – (Pyriproxifen & amitraz collars (Preventic PLUS®, Virbac), dogs only!, no longer available in the US, Pyriproxifen & 2% permethrin (KnockOut® Collar for Dogs, Virbac), no longer available in the US, Pyriproxifen (KnockOut® Cat & Kitten Collar for Dogs, Virbac), no longer available in the US)
Advantages – Ovicidal and larvicidal for fleas, UV stable juvenile hormone analogue, translocates to bedding, IGR efficacy for 3 months, Preventic Plus® adds tick protection
Disadvantages – long-term residual status may affect beneficial insects
Bottom-line – very useful adjunct to spot-ons or spray products, useful in dogs requiring frequent shampooing

Figure 1 (Continued).

Synthetic pyrethroid containing pump sprays (variety of manufacturers)
Advantages – Daily use in dogs requiring frequent shampooing
Disadvantages – Frequency of application, compliance, poor residual activity
Bottom-line – Rarely used as sole therapy unless very closed environment, use in dogs requiring frequent shampooing, compliance problems

Metaflumizone spot on preparation (ProMeris™ for cats, Fort Dodge; new product)
Advantages – Kills/debilitates adult fleas on contact, ease of application, stops egg production?
Disadvantages – Does not have repellent action, diminished efficacy after bathing or swimming?, does not have activity against ticks, application site reactions?
Bottom-line – New product awaiting judgment

Metaflumizone & Amitraz spot-on preparation (ProMeris Duo™for dogs, Fort Dodge; not yet available in US)
Advantages – Kills/debilitates adult fleas on contact, ease of application, stops egg production?, efficacy against ticks
Disadvantages – Dog only product, does not have repellent action, diminished efficacy after bathing or swimming?, application site reactions?
Bottom-line – Currently not available in the US

Pyriprole spot on preparation (PracTic, Novartis in Europe; not available in the US)
Advantages – Kills/debilitates adult fleas on contact, ease of application, efficacy against ticks
Disadvantages – Does not have repellent action, diminished efficacy after bathing or swimming?, application site reactions?
Bottom-line – Product not available in the US

Future flea products?
Lilly Companion Animal Health
Summit Vet Pharm

Figure 2. Modern Tick Control Products

Fipronil & S-Methoprene (Frontline® Plus, Merial), Fipronil (Frontline® Spray, Merial)
Advantages – Kills ticks, ease of application, residual activity, and also kills fleas
Disadvantages – Does not have repellent action, some diminished efficacy after bathing or swimming, occasional application site reactions
Bottom-line – Good product for tick control

Imidacloprid & 44% permethrin (Advantix®, Bayer)
Advantages – Kills ticks, ease of application, also kills fleas and mosquitoes
Disadvantages – Dog only product, do not use on cats, diminished efficacy after bathing or swimming, occasional application site reactions?
Bottom-line – Good broad-spectrum product, dog only product!

Selamectin (Revolution® [USA]; Stronghold® [Europe], Pfizer)
Advantages – Kills ticks, also broad spectrum against many internal and external parasites, kills adult fleas, kills some ectoparasitic mites (*Sarcoptes, Notoedres, Cheyletiella, Otodectes*), ease of application,
Disadvantages – Diminished efficacy after bathing or swimming, application site reactions?
Bottom-line – Good product for tick control

Amitraz- containing collars – (Preventic®, Virbac), dog only product
Advantages – Detaches and kills ticks, residual activity for 3 months
Disadvantages – Dog only product
Bottom-line – Good product for tick control

Metaflumizone & Amitraz spot-on preparation (ProMeris Duo™ for dogs, Fort Dodge; not yet available in US
Advantages – Kills ticks, also kills/debilitates adult fleas on contact, ease of application
Disadvantages – Dog only product, diminished efficacy after bathing or swimming?, application site reactions?
Bottom-line – Currently not available in the US

Figure 3. Modern Contagious Acarid Control Products

Selamectin (Revolution® [USA]; Stronghold® [Europe], Pfizer)
Selamectin is used for mite infestations most commonly at label dosages every 2 weeks for a minimum of 3 applications.

Advantages – Kills all 3 ectoparasitic mites, approved for use on dogs and cats, label claims, ease of application, and kills adult fleas and ticks, also broad spectrum against many internal and external parasites
Disadvantages – None
Bottom-line – Good product to treat small animal contagious acariasis

Ivermectin (Ivomec®, Merial; DVMectin®, DVM Pharmaceuticals)
Ivermectin (230 µg/kg or 1/10 cc/10 lbs body weight) is given per os for a minimum of four weekly dosages. Certain dog breeds are potentially more sensitive to this drug owing to the MDR1 mutation, which diminishes the efficacy of the blood-brain barrier. At the dosages used for scabies, this problem is of most concern for Collie Dogs and Shetland Sheep Dogs. Serious adverse neurologic reactions have been seen in Collie Dogs, Shetland Sheep Dogs, Border Collies, Australian Shepherds, and, less commonly, a variety of other breeds.

Advantages – Inexpensive, efficacious
Disadvantages – Toxicity in dogs with MDR1 mutation, Ivomec® is a product licensed for use in cows
Bottom-line – Efficacious product to treat small animal acariasis

Milbemycin oxime (Interceptor®, Novartis Animal Health)
Milbemycin, another avermectin, is also efficacious in treating acariasis. Recommended dosages vary from 1x to 2x the monthly heartworm dose given once weekly for four weeks. Milbemycin may be a 'safer' avermectin than ivermectin, but caution should still be exercised in at-risk breeds.

Advantages – Efficacious, licensed for use in dogs, more safe than ivermectin.
Disadvantages – Toxicity in dogs with MDR1 mutation
Bottom-line – Efficacious product to treat small animal acariasis

***Imidacloprid & Moxidectin* (Advantage Multi®, Bayer; Europe – Advocate®, Bayer)**

Advantages – Ear mites, sarcoptic acariasis?, other contagious mites?, approved for use on dogs and cats, also kills fleas
Disadvantages – Diminished efficacy after bathing or swimming?, does not have activity against ticks, application site reactions?
Bottom-line – New product to treat small animal contagious acariasis?

Amitraz (Mitaban®, Pharmacia & UpJohn)
Amitraz is an MAO inhibitor and should not be used on dogs or applied by people taking other MAO inhibiting drugs. Amitraz should not be used on cats. Amitraz rinsing should be performed in well-ventilated areas. Rubber gloves should be worn by the applier.

Advantages – Efficacious, licensed for use in dogs
Disadvantages – Greater potential for toxicity
Bottom-line – Other products with equal or greater efficacy have less potential for toxicity

ESTABLISHING THE DIAGNOSIS OF FLEA ALLERGY DERMATITIS & CONVINCING THE OWNER

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Pruritus is the predominant clinical sign of allergic skin disease in both the dog and the cat. Pruritus together with associated self-trauma also is the most common reason globally for a dog to be presented to a veterinary hospital. The "Threshold Phenomenon" is important in understanding pruritus. An animal or person may tolerate a certain pruritic load without provoking clinical signs but a minor increase in "pruritic load" may push an animal over the threshold thus initiating pruritus. "Summation of Effect" occurs when additive pruritic stimuli from multiple diseases raises an animal above its individual pruritic threshold. As an example, the pruritus from flea allergy dermatitis, atopic dermatitis, and secondary infections all are additive.

Globally, the most common allergic canine skin diseases are, in frequency of occurrence, flea allergy dermatitis, atopic dermatitis, and food allergy. Flea allergy dermatitis (FAD) is not only the most common skin disease seen in general small animal practice in most countries in the world; it most likely is the most common disease of any organ system seen in small animal practice worldwide. Somewhat surprisingly, flea allergy dermatitis still is seen relatively commonly in university dermatology clinics and dermatology specialty practice worldwide. This occurs despite modern advances in flea control plus the fact that most small animal clinicians are quite cognizant of flea allergy dermatitis and routinely manage dogs and cats with flea allergy dermatitis. Self-referral by the owner (second opinion) or veterinary referral of dogs and cats with flea allergy dermatitis occurs for multiple reasons. Surprisingly, when you suspect flea allergy, your most important task is convincing the owner that you are making the correct diagnosis.

DIFFERENTIATING FAD FROM OTHER ALLERGIES

There are no laboratory tests available that definitively rule in or rule out allergic skin disease. Since flea allergy dermatitis is the most common allergic skin disease, it is logical to rule out flea allergy first by several months of strict flea control. Remember that dogs with one allergic skin disease are more likely to have other allergic skin diseases.

Signalment Predilections

Flea allergy dermatitis can be seen in any breed, but it is more common in "allergic breeds" that commonly develop atopic dermatitis and food allergy. Flea allergy is more common in dogs over 6 months of age. Sex predilections have not been reported.

Speed of Onset

Flea allergy dermatitis usually is of rapid onset. Atopic dermatitis usually is insidious and gradual in onset. Food allergy usually is insidious and gradual in onset, but occasionally may be more rapid in onset.

Seasonality Predilections

Flea allergy dermatitis is contingent on flea availability which depends on weather, seasonal temperature and humidity changes, and severity of winters. Atopic dermatitis commonly may begin seasonally (summer), but annually adds time in the spring and fall and finally becomes year-round. Food allergy should not be seasonal.

REASONS WHY FAD IS SEEN IN DERMATOLOGY SPECIALTY PRACTICE

It seems counterintuitive that FAD is seen commonly in dermatology specialty practice. In the author's opinion, the three most common reasons that this occurs are (1) owner disbelief that flea allergy is the correct diagnosis, (2) owner skepticism that flea allergy is the correct diagnosis based on the failure of past therapy, and (3) veterinary practitioner skepticism that FAD is the correct diagnosis based on past therapeutic failure or the lack of visualization of fleas.

OWNER DISBELIEF IN THE DIAGNOSIS OF FAD

Failures in the management of flea allergy dermatitis correlate strongly with owner disbelief that fleas are the underlying problem. We frequently hear the statement, "My veterinarian believes that the problem is due to fleas but I *know* that it is not!" Reasons for this disbelief include:

1. Fleas not seen by the owner
2. Cultural biases against having ectoparasites – "It is not acceptable for me to have ectoparasites. Therefore it is not acceptable for my dog to have ectoparasites!"
3. The attitude that "How can fleas cause this much trouble?"
4. The thought that "All dogs have fleas."

OWNER OR VETERINARY SKEPTICISM BASED ON THE FAILURE OF PAST THERAPY

We regular hear the following comments from owners: "I am already doing everything that I can to kill fleas!" and "We are already using the latest wonder drugs!". Usually we find multiple errors in their flea control program.

REASONS FOR FAD TREATMENT FAILURE

The most common reasons for therapeutic failure include

1. Failure to treat *all* in-contact animals (the squeaky wheel gets the oil... indoor-outdoor cats, regular animal visitors that are not receiving flea control)
2. Failure to use flea control products properly
3. Failure to maintain consistency in treatment
4. Failure to deal with environmental issues in severe cases
5. Substitution of prescription spot-ons with less expensive, but less effective and less safe 'spot-on' products from pet stores

CLINICAL FEATURES OF FAD THAT MAY BE USEFUL IN CONVINCING THE OWNER

The pruritus seen with FAD is predominantly localized to the caudal half of the dog. FAD has a characteristic distribution pattern with partial bilateral symmetry and lesions involving the dorsal lumbosacral region, tail-base, perineum, and medial and caudal thighs. The lesions of FAD include crusted papules, erythema, and excoriations. Secondary or chronic changes include lichenification, hyperpigmentation, alopecia, fibropruritic nodules, and secondary organism overgrowth or infection. Crusted papules in the umbilical fold, especially in male dogs, are an under-appreciated clinical marker of FAD. Fibropruritic nodules are highly characteristic clinical markers of FAD in dogs predisposed to their development. Secondary bacterial or *Malassezia* overgrowth or infections are underappreciated causes of increased pruritus in all allergic skin diseases including FAD.

TECHNIQUES FOR CONVINCING OWNERS THAT FAD IS THE APPROPRIATE DIAGNOSIS (BACKING INTO THE DIAGNOSIS)

We never begin by simply telling the owner that their dog has FAD. During the time that we are establishing rapport with the owner, taking the history, performing the physical examination, and taking surface cytology specimens and evaluating them microscopically, we draw an imaginary line around the middle of a dog and ask the owner; "Does your dog itch more in front of or behind this line?" (Flea allergy dermatitis is the *only* known canine pruritic skin disease seen consistently with a markedly caudal bilaterally symmetric distribution pattern.)

At that point, we briefly discuss with the owner how a diagnosis is made, mentioning lesions, distribution pattern, frequency of occurrence, and ruling out other diseases. We then define allergy and talk about the three most common allergic skin diseases seen in dogs (atopic dermatitis, food allergy, flea allergy). Within that discussion, we talk about flea allergy being an allergic reaction to proteins in the saliva of the flea and tell them that there are at least four different types of allergic reaction to flea antigen that determine the severity of the allergic response. We also indicate that we tend to see severe flea allergy in well-cared-for animals living in clean environments that have limited exposure to fleas. During this discussion, we describe the distribution pattern of the three common allergic skin diseases and gradually let the owners draw their own conclusions about which pattern their own dog best fits. It also is beneficial to show them how many of the possible reasons for FAD treatment failures were present in their previous overall flea control methods.

The presence of ectoparasites on either humans or animals is a hot-button issue in developed, industrialized countries. People do not consider it appropriate to have ectoparasites either on themselves or on their animals. This cultural bias is pervasive, strong, and not particularly rational. One must find a method of diffusing this cultural bias and the hostility that can come with it. In California, we may say, "Fleas are a way of life in ______. My own dogs acquire fleas if I don't practice strict flea control routinely and consistently." The key is getting the owner to buy into the possibility that their dogs pruritus is due to a severe hypersensitivity to the bites of fleas. Again, this includes showing them the possible reasons for previous treatment failures. We also discuss the importance of ruling out "the most common allergic skin disease" before expensive or time consuming testing. We then offer the owners the alternative of 6 weeks of concerted flea control based on our recommendations. Lastly, if this is not working, our final gambit is *not*, "Trust us". Instead it is "Prove us wrong"!

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CHALLENGES IN THE MANAGEMENT OF DEEP PYODERMA

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Pyoderma is second most common cause of canine skin disease. In areas of the world that are less favorable to fleas, pyoderma is the most common canine skin disease. We can define pyoderma as a pyogenic or pus-producing bacterial infection of the skin. Dogs seem uniquely susceptible to both single-event pyoderma and recurrent pyoderma. The reasons for this may relate to various host factors that could result in enhanced susceptibility to infection. These factors could include the comparatively thin, compact stratum corneum of dogs, the relative lack of intercellular lipids in the canine stratum corneum, the lack of a lipid-squamous epithelial plug in the entrance of canine hair follicles, and the relatively high pH of canine skin.

The diversity of canine pyoderma is enormous. Classification of pyoderma is most usefully based on depth of bacterial involvement as it provides information on diagnosis, differential diagnosis, likelihood of underlying disease, prognosis, and likely response to therapy. Pyoderma may be *surface*, affecting the stratum corneum and outer epidermis; *superficial,* involving only the epidermis and the epithelial appendages in the dermis; or *deeper*, compromising structures in the dermis and the deep, subjacent fatty tissue. As we gain knowledge about canine skin infections, we realize that most infections seem to be secondary to either underlying disease or other underlying factors that somehow increase the likelihood of infection. Few pyoderma are "primary" and do not have underlying causes or triggers. If underlying causes are not found, it is likely that recurrence will follow seeming cure. This recurrence suggests that the initial infection was not "primary" but more likely was secondary to undiagnosed underlying disease or unrecognized triggering factors. Superficial pyoderma are more common than deep pyoderma. As infection proceeds deeper into hair follicles, follicular rupture leads to a granulomatous foreign body tissue response. Deeper infections require a more aggressive diagnostic and therapeutic approach.

Staphylococcus intermedius is by far the most common pathogen in canine pyoderma. Less commonly, *Staphylococcus aureus* and *Staphylococcus schleiferi* may cause canine skin infection. Gram-negative organisms such as *Proteus* sp., P*seudomonas* sp., and *Escherichia coli* are more likely to be secondary invaders in deep pyoderma. Rarely, *Pseudomonas aeruginosa* and other gram-negative organisms can be the sole pathogen. Unusual staphylococcal infection or gram-negative organisms are more likely to be more resistant to various antibiotics.

MICROBIAL RESISTANCE TO ANTIBIOTICS

Microbial resistance in staphylococci is increasing. **Methicillin resistance** has greatly complicated the use of antibiotics in human medicine. Methicillin resistance is being recognized with increased frequency in veterinary medicine and will have substantial impact on how we manage skin disease caused by staphylococcal species in the future. Methicillin resistance is reported in *Staphylococcus aureus* (hospital acquired or community acquired HA-MRSA & CA-MRSA), *Staphylococcus intermedius* (MRSI), and *Staphylococcus schleiferi* (MRSS).

Empirical treatment of staphylococcal infection has been the norm in veterinary dermatology. Only refractory cases have been cultured routinely. This probably has lead to the lack of identification of methicllin-resistant strains. We may be reaching the day when bacterial culture and sensitivity should be recommended for all pyoderma that have not responded to appropriate initial empirical antibiotic therapy.

Emerging concepts that aid in the understanding and management of deep pyoderma include quorum sensing, biofilms, the mutant selection window hypothesis, and the mutant prevention concentration (MPC).

Quorum sensing is a mechanism by which bacteria produce and secrete various signaling compounds (autoinducers) that bind to receptors on other bacteria and activate transcription of genes. This process is responsible for communal behavior among bacteria and offers clues into the processes of symbiosis, commensalism, and pathogenicity. Unlocking the mechanisms of quorum sensing may offer new methods of controlling infection such as disruption of quorum sensing pathways.

Biofilms are aggregates of organisms that form on interfaces. These aggregates are much more protected from the toxicity of antimicrobials or the host immune response and hence are much more difficult to control. Once established, biofilms initiate a range of surface-associated and diffusible signals, which may moderate the settling behavior of other organisms.

The **mutant selection window hypothesis** states that a "dangerous drug concentration zone" exists and that exposure to antimicrobial concentrations inside this zone confers a survival advantage to organisms having reduced susceptibility. The lower boundary of the selection window is approximately the MIC (mean inhibitory concentration) and the upper boundary is termed the MPC (mutant prevention concentration). When an antibiotic is dosed at the top of the MIC, the first decline in organism concentration corresponds to the MIC of the wild-type bacteria. The following plateau is due to the presence of resistant mutant subpopulations. The second drop in organism recovery arises when the MIC of the least susceptible mutant is reached. This latter value is termed the MPC. Above the MPC, an organism must acquire two concurrent resistance mutations for growth to occur (very rare event). Within the mutant selection window, the range of drug concentrations exert selective pressure on microbial growth and cells that harbor resistance genes grow preferentially. Dosing guided by traditional pharmacodynamics standards places antimicrobial concentrations within the mutant selection window, thus selectively enriching resistant mutant subpopulations.

There is much interest in human medicine on dosing at or above the MPC. Newer drugs with pharmacologic properties that allow safe dosing above the MPC will likely become more important in the management of all infections.

COMMON COMPLICATING FACTORS

Both treatment failure and recurrence of infection are associated with lack of recognition of factors that influence prognosis and complicate management of all pyoderma. The most common complicating factors include inappropriate initial therapy, unidentified coexisting and underlying skin diseases, and external environmental factors such as poor owner compliance.

Inappropriate initial therapy includes errors in antibiotic selection, dosage, and duration of therapy. If cytology shows infection to be due to cocci and antibiotic choice is empiric, an antibiotic must be selected with a known spectrum of activity directed against *Staphylococcus intermedius*. Lack of response should initiate culture and sensitivity. Under-dosing leads to diminished therapeutic efficacy and overdosing is more likely to cause adverse reactions and needlessly increases expense. Under-dosing is common in larger dogs and overdosing is more common in small dogs. Systemic antibiotics should be utilized for a minimum of 3 weeks for superficial and 6 weeks for deep pyoderma. In general, antibiotics should be continued for a minimum of 1 week beyond apparent clinical cure in superficial pyoderma and 3 weeks beyond clinical cure for deep pyoderma.

Unidentified persistent underlying skin diseases that may complicate the initial management of pyoderma or lead to recurrence of infection include non-parasitic allergic skin diseases (canine atopic dermatitis, food allergy), parasitic allergic skin diseases (flea allergy dermatitis, sarcoptic acariasis, cheyletiellosis), demodicosis, endocrine diseases (hypothyroidism, hypergluco-corticoidism—primary or iatrogenic), diseases of cornification ("primary seborrhea"), genodermatoses affecting the hair follicles or adnexa (follicular dysplasia, color dilution alopecia, sebaceous adenitis), other infectious skin diseases (*Malassezia* dermatitis), occult neoplasia (solar-induced squamous cell carcinoma), and immunodeficiency (congenital, acquired).

External environmental factors that influence therapeutic success include owner compliance, loss of drug via vomition, and unexpected drug inactivation. Owner compliance is largely unexplored in veterinary medicine. In human medicine, it has been published that only 40% of prescriptions are even filled and only 40% or less of medication received is taken appropriately! Based on studies performed in human medicine, it is likely that compliance is enhanced when drugs are dispensed that need to be administered only once daily. This may contribute to a perceived enhanced efficacy in once-daily antibiotics such as enrofloxacin, marbofloxacin, cefpodoxime, and ormetoprim-potentiated sulfadimethoxine. Twice-daily products such as cephalexin, lincomycin, and clindamycin also may offer advantages over antibiotics requiring administration three times daily.

The management of deep pyoderma offers additional challenges. Deep follicular inflammation frequently leads to follicular rupture and furunculosis. Granulomatous foreign body response directed against free keratin from the root sheath and hair shaft fosters the scar tissue formation and sequestered pyogranulomas. Consequentially, the dual problems of infection and foreign body granulomas coexist. Unidentified or unsuccessfully managed persistent underlying skin diseases are much more likely to be present with deep pyoderma. Additional challenges include antibiotic dosage problems, the impact of sequestered foci of infection, inactivation of the antibiotic by pus and inflammatory products, and the possibility of unidentified mixed bacterial infection with aerobic or anaerobic organisms.

Unidentified or unsuccessfully managed persistent underlying skin diseases that most commonly complicate the management of canine deep pyoderma include demodicosis, hypothyroidism, iatrogenic hypergluco-corticoidism (especially associated with long-term management of allergic skin diseases), genodermatoses affecting the hair follicles or adnexa such as color dilution alopecia and sebaceous adenitis, occult neoplasia such as solar-induced squamous cell carcinoma, and either congenital or acquired immunodeficiency.

Occult demodicosis is a commonly undiagnosed initiator of deep pyoderma. Unexplained pyoderma in unusual locations such as the head and face should cue the clinician to look for demodicosis. Index of suspicion for demodicosis may be low in small long-hair-coated breeds. Hair loss is not a prime sign of demodicosis in these breeds that have long anagen hair cycles.

Hypothyroidism may allow bacterial infection to invade deeper into the skin. Contributors to immune surveillance deficits such as hypothyroidism should be investigated in any dog with unexplained deep infection or infection that becomes more generalized then most pyoderma.

Iatrogenic hyperglucocorticoidism is a common and subtle occurrence noted in the long-term management of allergic skin diseases and other non cutaneous diseases. All dogs receiving long-term oral or parenteral corticosteroids and small dogs (less than 8 kg.) receiving topical, aural or ophthalmic corticosteroids should be suspected of iatrogenic hyperglucocorticoidism if pyoderma is unexplainably widespread or invades more deeply that expected.

Genodermatoses affecting the hair follicles or adnexa such as color dilution alopecia and sebaceous adenitis are underdiagnosed initiators of deep pyoderma. Any anatomic defect in hair follicles predisposes to both superficial and deep folliculitis. Color dilution alopecia is seen most commonly in blue and fawn Doberman Pinschers but has been reported in many other breeds. Breed predilections for sebaceous adenitis, another follicular genodermatosis, have been noted for Standard Poodles, Samoyeds, Akitas, and Vizslas. The disease also has been reported in other breeds.

Solar-induced skin disease in regions of the world with intense solar exposure is underdiagnosed. It occurs in non-pigmented and lightly haired skin exposed repetitively to excessive ultraviolet light. Affected dogs commonly have a history of sunbathing. Multiple stages of premalignant change (solar keratosis) and malignant transformation to invasive squamous cell carcinoma occur concurrently. Dalmatians, Whippets, Italian Greyhounds, Greyhounds, American Staffordshire Terriers, "Pit Bulls," Bull Terriers, Beagles, and Basset Hounds are at increased risk.

Congenital or acquired immunodeficiency may initiate deep pyoderma or make cure more difficult. Acquired immunodeficiency may be seen in conjunction with underlying diseases such as neoplasia (especially lymphosarcoma) or immunosuppressive therapy.

ANTIBIOTIC THERAPY

Most antibiotic dosages recommended for the treatment of pyoderma are largely empiric. Clinicians commonly use the same dosages of antibiotics for both superficial and deep infection. This can lead to the belief in increased resistance of *S. intermedius*. Flexible dosage recommendations for different infections should lead to greater awareness of under-dosing of dogs with deep pyoderma.

In deep pyoderma, sequestered foci of infection impede antibiotic penetration, and keratin debris from ruptured hair follicles encourages foreign body granulomatous response. Granulomatous inflammation prevents antibiotic access to sites of infection. Antibiotics such as penicillins that require microbial replication for activity are less likely to be effective when necrotic tissue and obstructed drainage routes create conditions that are no longer favorable for bacterial multiplication. Consequently, higher antibiotic dosages are warranted in the management of chronic deep pyoderma.

Unidentified mixed bacterial infection with anaerobic as well as aerobic organisms is largely unexplored in the study of canine pyoderma. Recent data in human medicine suggests that anaerobic bacteria may play a larger roll in deep infections that respond slowly or poorly to antibiotic therapy.

Clinicians confronted with canine deep pyoderma should always ask themselves the question, 'Why?' If an underlying management error or an undiagnosed underlying disease is present, success in managing deep pyoderma is low.

Successful management of all deep pyoderma requires systemic antibiotic therapy. Topical antibacterial shampoo therapy commonly is used as an adjunct in the management of deep pyoderma to speed recovery, improve patient well-being and attitude, encourage owners, and potentially prevent recurrence. Immunomodulatory therapy is used less frequently and usually is an attempt to prevent or diminish the frequency of recurrent superficial infection. Extended regimens of antibiotics are used as a last resort in the management of frustrating recurrent infection.

The basic principles of successful systemic antibiotic therapy including selection of an appropriate antibiotic, the establishment of an optimal dosage, and the maintenance of that dosage for enough time to ensure cure rather than transient remission. Surface lesions in deep pyoderma commonly heal more rapidly than deeper lesions, although sequestered foci of infection may not be visible. Antibiotic selection can either be empiric or based on bacterial culture and susceptibility testing. An antibiotic chosen empirically should have a known spectrum of activity directed against *S. intermedius* and, should not be inactivated by beta-lactamases.

Bactericidal antibiotics are recommended for deep pyoderma and when immunosuppression is confirmed or suspected. Pustules or fistulous tracts should be recultured if *S. intermedius* has not been isolated as the primary pathogen. If multiple isolates are not sensitive to one oral antibiotic, an antibiotic that is effective against *S. intermedius* should be instituted since staphylococci create a tissue milieu favorable to the replication of secondary bacterial invaders.

Antibiotics most likely to be successful in the management of deep pyoderma include cephalexin, enrofloxacin, marbofloxacin, cefpodoxime, clindamycin, oxacillin, and clavulanate-potentiated amoxicillin. More resistant *S. intermedius* and gram-negative isolates are seen more commonly in referral practices than in general practice, and resistant bacterial populations are identified most frequently in deep pyoderma.

Chronic, deep pyoderma requires antibiotic penetration as sequestered foci of infection and scarring prevent antibiotic access to the site of infection. First-generation cephalosporins such as cephalexin have good to very good penetrating ability. Cefpodoxime also offers very good penetration. Uptake of enrofloxacin by macrophages was shown to concentrate that antibiotic at the site of deep granulomatous infection thus leading to potent tissue-penetrating abilities. Similar or even better attributes may apply to other new generation fluoroquinolones that are on the horizon. Fluoroquinolones also offer the advantages of once-daily dosing, activity against both *S. intermedius* and gram-negative secondary invaders, and diminished likelihood of resistance. Once-daily dosing with fluoroquinolones is strongly recommended because the bactericidal effect is concentration rather than time dependent.

ADJUNCTIVE THERAPY

Antibacterial shampoos are used as adjunctive therapy in the management of deep pyoderma. Antibacterial shampoos aid in debridement, encourage drainage, and decrease pain. The mechanisms of action is to decrease surface bacterial counts and to limit bacterial recolonization, hopefully diminishing the likelihood of recurrent infections. Improvement in patient attitude and owner encouragement are additional benefits. Antibacterial shampoos contain benzoyl peroxide, benzoyl peroxide and sulfur, chlorhexidine, ethyl lactate, or triclosan. Twice-weekly antibacterial shampoos are the most common recommendation. More aggressive topical therapy is beneficial for the management of deep pyoderma. After clipping, dogs benefit from daily antibacterial shampoos or twice-daily whirlpools. Chlorhexidine is added to warm water. Although labor intensive, whirlpools remain an under-employed but highly beneficial modality of topical therapy for deep pyoderma.

All dogs with pyoderma should be re-evaluated within 2 to 3 weeks. If substantial improvement is not noted, the clinician should consider factors that may have complicated management. Owner compliance to the appropriate dosage and drug loss through vomiting, inactivation by food, or malabsorption are common reasons for failure. Referral to a veterinary dermatologist should be considered each time that clinical failure occurs.

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DIAGNOSIS AND TREATMENT OF MANGE

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The diagnosis of skin disease is often difficult due to the similarity of clinical signs of many dermatoses. A thorough history can be extremely helpful in establishing a diagnosis in veterinary dermatology. Breed predispositions exist for canine demodicosis, young dogs tend to present with ectoparasites more commonly, acute onset of pruritus is frequently seen with scabies, some mites such as ear mites, *Sarcoptes* and Cheyletiella are contagious, the latter two may affect owners as well, and so on. Lesion localization often also gives clinical clues (Table 1).

The primary lesion of canine demodicosis is a follicular papule or pustule (for which there are only two main differentials, bacterial folliculitis and dermatophytosis). Scabies typically presents with nonfollicular papules, cheyletiellosis typically with scaly dermatitis. Ear mites can often be seen with otoscopic examination; the copious coffee-ground debris is classic and can be scooped up and evaluated in mineral oil under the microscope.

DIAGNOSTIC TESTS FOR ECTOPARASITES IN SMALL ANIMAL PRACTICE

Superficial skin scrapings are taken from large surface areas, usually to detect *Sarcoptes* or *Cheyletiella*. Elbows, hocks, ear margins and the abdomen are commonly scraped for *Sarcoptes* mites, the dorsal trunk for *Cheyletiella* mites. Scrapings are performed in the direction of hair growth; 50% of scabies cases may be negative on several scrapings. One mite or egg is diagnostic. It is important to scrape over a large area and in hairy dogs this may be easier if the hair is clipped away first. I use scissors to remove the hair and select non-excoriated sites preferably with scale and papules as the lesions. Mineral oil is then applied directly to the affected skin, gently scraped off the surface, put on a slide, a cover slip is applied and the sample is evaluated microscopically. This technique produces more slides to evaluate, but seems to have a higher diagnostic efficacy.

Deep skin scrapings are performed to detect *Demodex* mites. It is useful to squeeze the skin prior to the scraping in an attempt to push the mites out from the depths of the follicles. A blade covered with mineral oil should be used in the direction of hair growth until capillary bleeding is observed. More than one mite is diagnostic. When evaluating *Demodex* scrapings it is important to assess **and to record** both the site of scraping and the relative numbers of adults, larvae / nymphs and eggs. In subsequent visits assessment of response to therapy relies on the comparison of such numbers, I routinely repeat scrape the same sites on a monthly basis when monitoring my demodicosis cases.

Trichograms or hair plucks may render skin scrapings unnecessary in areas that are difficult to scrape such as the eye lids, periocular area, muzzle or feet. A forceps is used to pluck hairs in a partially alopecic area. The hairs are then placed onto a slide and evaluated under low power. If *Demodex* mites are found, skin scrapings are not necessary. This is particularly useful when sites close to the eyes are affected or the lesions are very painful.

Tape preparation is a direct impression technique using clear sticky tape to collect debris from the surface of the skin. The tape is pressed several times sticky side down onto the skin. Next, it is pressed (also sticky side down) onto a slide. The tape serves as its own cover slip. This technique is especially useful for *Cheyletiella* mites, short-bodied *Demodex* mites and occasionally even *Sarcoptes* mites, as a larger surface area can be sampled very quickly.

Table 1. Localization of Lesions and/or Pruritus of Various Skin Diseases

Localization of Lesions and/or Pruritus	Common Underlying Diseases
Otitis externa	Atopy, adverse food reaction, endocrine diseases **Ear mites** Secondary infections
Pinnae	Atopy, adverse food reaction **Scabies** Vasculitis, pemphigus
Head/face	**Demodicosis** Atopy, adverse food reaction *Microsporum gypseum* Insect allergies
Paws	**Demodicosis** Atopy, adverse food reaction Malassezia dermatitis Pemphigus

SCABIES

Scabies is a contagious disease caused by *Sarcoptes scabiei* var. *canis* in dogs and by *Notoedres cati* in the cat. The mite does not survive off the host for very long periods of time. Clinically, scabies is characterized by tremendous pruritus. Papules, scales and crusts develop at affected sites, typically the elbows, hocks, face and pinnae in the dog and the face, ears and neck in the cat. Any pruritic dog or cat could possibly be infested with *Sarcoptes scabiei* or *Notoedres cati* respectively, particularly if the pruritus was of sudden onset or if pinnae, ventrum and elbows are pruritic. Negative superficial skin scrapings do not rule out scabies, thus trial treatment is indicated in any patient with suspected scabies irrespective of negative skin scrapings. In Europe, where a highly sensitive and specific serum test is available, trial therapy still holds an important place in the diagnosis of scabies, as the tested anti-scabies antibodies take several weeks to reach diagnostic concentrations.

EAR MITES

These are large, white and freely moving mites with four pairs of legs extending beyond the body margin (except the rudimentary fourth pair of the female). The mites feed on epidermal debris and tissue fluid from the superficial epidermis. They cause intense irritation and thick reddish brown crusts in the ears of dogs and cats. Mites are commonly found on other areas of the body, especially the neck, rump and tail. The parasites are highly contagious. Infestations of cats vary from country to country with values as low as 3.5% in Australia and as high as 75% in the States.

CHEYLETIELLOSIS

Cheyletiella ("Walking Dandruff") are large mites (385 µm) that affect cats (*C. blakei*), dogs (*C. yasguri*), rabbits (*C. parasitovorax*) and humans (transiently affected by *C. yasguri* or *blakei*). The yellowish adult mites move rapidly in the stratum corneum but do not burrow. They live on tissue fluid released when they periodically pierce the skin. The ova are smaller than louse nits and are attached to hairs by fine fibrillar strands (not cemented firmly to the hairs as nits). The clinical course in small animals is chronic and typically relatively mild, but may be severe and generalized in 2- to 8-week old puppies. Older individuals may become asymptomatic carriers. Frequently scaling is the only change (due to mites and keratin scales) with mild to no pruritus noted. Cats may develop widespread papulocrustous eruptions and severe pruritus in some cases.

Treatment of Superficial Mites

- Selamectin is a spot on registered for the treatment of scabies and ear mites in many countries. It also has been shown to be effective against cheyletiellosis. I use it every 2 weeks for 3 treatments.
- Moxidectin is available as a spot-on registered for the treatment of canine scabies as well.
- Topical treatments include lime sulfur dips, amitraz, ivermectin and other antiparasitic rinses. They are used weekly for 4 weeks.
- Systemic therapy may be undertaken with ivermectin or milbemycin. The routine protocol for a dog which has never previously been treated with ivermectin before, is a slow increase from 50 µg/kg on day 1 to 100 µg/kg on day 2 to 150 µg/kg on day 3 to 300 µg/kg on day 4. The owners are carefully educated to the above mentioned side effects. If any signs of ataxia or tremors occur, administration of the drug must be discontinued immediately. Once the maintenance dose is reached, we continue that dose once weekly for 3 more weeks in suspected or proven cases with scabies, cheyletiellosis or infestations with *Otodectes cynotis*. Giving milbemycin oxime at 2 mg/kg twice weekly for 3 to 4 weeks has also proven a very safe, easy and successful treatment protocol for canine scabies.
- All animals in contact with the patient need to be treated as well!
- Initial deterioration during the first days of treatment may occur and may be treated with glucocorticoids daily for 3 to 4 days at up to 1 mg/kg body weight.

DEMODICOSIS

Demodex canis is an obligate parasite of the dog and low numbers of mites are part of the normal cutaneous fauna. The life cycle involves fusiform eggs hatching into six-legged larvae, molting into eight-legged nymphs and finally maturing into adults. In the dog, *Demodex canis* is the most commonly recognized mite, but a short-bodied and a long-bodied *Demodex* species have also been described. When considering the pathogenesis of demodicosis in dogs, it is important to distinguish between juvenile onset and adult onset generalized disease. In the former, certain breeds are at increased risk. Analysis from two kennels suggested an autosomal recessive mode of inheritance. Other predisposing factors mentioned in the literature include short hair, poor nutrition, stress, estrus, endoparasites, and debilitating disease. Adult-onset demodicosis can be triggered by drugs or diseases which have altered the immune response. Hypothyroidism, hyperadrenocorticism, leishmaniasis, glucocorticoid therapy, neoplasias or chemotherapy have all been reported in dogs with adult-onset demodicosis, although idiopathic adult-onset demodicosis occurs. In cats, demodicosis is typically due to an underlying systemic disease!

Clinically, canine demodicosis is characterized initially by follicular papules. However, erythema, comedones, pustules and crusting all may occur and any dog with lesional skin disease should be scraped for demodicosis. Lesions can occur anywhere on the body, although the face and feet are mot commonly affected. The treatment of generalised demodicosis is outlined below. Lime sulfur rinses (2%) weekly for 4 to 8 weeks are recommended for the treatment of feline demodicosis.

Amitraz is effective against demodicosis, scabies, *Cheyletiella* spp, and *Otodectes cynotis*. The adverse reactions associated with amitraz administration or application are sedation, bradycardia, hypothermia, hypotension, bloat, polyuria, vomiting and hyperglycemia. Clipping the entire dog is essential to allow better contact of amitraz with the skin. All crusts should be removed (preferably by shampooing with an antibacterial follicular flushing agent such as benzoyl peroxide). The dog has to be dry completely (2–8 hours), before being sponged with amitraz. The person applying the treatment should wear protective gloves and work in a well-ventilated area. At my clinic, owners with asthma are advised to find somebody else for the rinses. The dog should stand in a tub with its feet in the amitraz solution to allow soaking of the often extensively affected feet. Amitraz causes a transitory sedative effect for 12 to 24 hours. Concentration of the drug and frequency of application influences the response rate. I use a concentration of 600 ppm once weekly. For pododermatitis and otitis externa, a mixture of 1 mL of amitraz with 30 mL of mineral oil can be used topically on a daily basis. Treated dogs should not get wet or be washed and should avoid contact with water or wet grass.

Ivermectin orally at 300 to 500 µg/kg daily is used in the treatment of demodicosis and scabies with good success. It must not be used in Collies and Old English Sheep dogs, as it commonly causes adverse reactions in these breeds. They include ataxia, mydriasis, tremors, stupor, salivation, bradycardia and respiratory arrest. In my practice I have seen other breeds affected as well showing ataxia and tremors at lower doses. Thus, the routine protocol for a dog that did not receive ivermectin previously, is a slow increase from 50 to 100 µg/kg to 150 to 300 µg/kg on subsequent doses every day. The owners are avised to monitor the animal carefully during that time for the above mentioned side effects. If any signs of ataxia or tremors occur, administration of the drug must be discontinued immediately. Once the maintenance dose is reached, demodectic patients receive that dose once daily until 4 weeks after the second consecutive negative monthly skin scraping.

Moxidectin is another milbemycin that was evaluated for the therapy of canine generalized demodicosis. Three studies have evaluated moxidectin at 200 to 400 µg/kg/day orally, two of which employed the initial gradual dose increase advocated for ivermectin. Reported side effects were ataxia, lethargy, inappetence and vomition. As moxidectin is a macrocyclic lactone and has a similar mode of action to the other drugs in this group, the success rate and rare adverse effects are not surprising. However, more studies with longer follow-up period periods are needed to identify potential benefits and disadvantages of this drug.

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A SYSTEMATIC REVIEW OF INTERVENTIONS FOR CANINE ATOPIC DERMATITIS

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Canine atopic dermatitis (CAD) is one of the more common skin diseases in small animal practice and in many respects similar to the frequently diagnosed atopic dermatitis in humans. A number of drugs have been reported as successful treatment for this disease in human and veterinary medicine, but in contrast to the human side, many treatment modalities have not been evaluated carefully with randomized controlled trials (RCT) in the veterinary field. A recent paper has attempted to systematically review most therapies in an evidence-based fashion.[1] This article will summarize the results of therapeutic trials using glucocorticoids, calcineurin inhibitors, antihistamines, fatty acids, leukotriene and phosphodiesterase inhibitors, prostaglandin analogues, allergen-specific immunotherapy (ASIT) and topical therapy for canine atopic dermatitis.

It has to be noted that validated clinical scoring systems for CAD were not developed until recently and have only been used in the last decade. In addition, evaluation of pruritus is difficult and subjective. Good validated scoring systems are not available at this point. It is hoped that the International Task Force of Canine Atopic Dermatitis will develop recommendations for such validated scoring systems in the next few years.

GLUCOCORTICOIDS

There is only one RCT evaluating topical 0.015% triamcinolone acetonide. After 4 weeks, clinician-assessed overall scores and owner-assessed pruritus scores decreased by 67% and significantly more than with placebo treatment. Adverse effects were lower than in the placebo group. Oral glucocortocoids typically were evaluated as standard-of-care controls in RCTs for comparison with other interventions and methylprednisolone, prednisone and prednisolone at 0.4 to 1 mg/kg/day were most commonly used. At the end of 4 to 16 weeks of treatment, lesion scores were reduced from 45% to 83% and pruritus by 33% to 81%. Adverse effects included polyphagia, polyuria/polydipsia (PU/PD), weight gain and/or intermittend GI signs. There is *good evidence for high efficacy* of oral and topical glucocorticoids and low harm of short term treatment. The benefit of long-term treatment with glucocorticoids must be weighed against the risk of adverse drug effects impacting on health and quality of life.

CALCINEURIN INHIBITORS

Oral cyclosporine is probably the most thoroughly evaluated drug for the treatment of canine atopic dermatitis. Three large blinded trials have been conducted with several hundred dogs. Cyclosporine at 5 mg/kg/day was found to be equally effective as prednisolone and methylprednisolone. After 6 weeks of treatment the reduction of clinician-graded lesion scores was 52% to 67%. Similarly, decrease of owner-assessed pruritus was 36% to 100%. Vomiting and diarrhea were the most commonly seen adverse effects and seen in 14% to 42% but were mostly mild to moderate and a reason for cessation of therapy in less than 1% of the patients. Papillomatous eruptions and gingival hyperplasia were also seen occasionally. The trials provided *good evidence for high efficacy* of oral cyclosporine in canine atopic dermatitis and are documented in a recent meta-analysis. However, the long term safety of cyclosporine in dogs is not known beyond the safety studies of cyclosporine treatment for one year in Beagle dogs.

Topical calcineurin inhibitors are registered for the treatment of human atopic dermatitis. Tacrolimus lotion was evaluated in several studies. At a concentration of 0.1%, it decreased clinician–assessed lesion scores and owner-assessed pruritus scores of localized atopic dermatitis by 60% to 63% and 58%, respectively, after 4 to 6 weeks of once to twice daily therapy. The only adverse effect seen in the studies using tacrolimus was mild and transient irritation at the site of application. These trials provide *good evidence for medium efficacy* of 1% tacrolimus in CAD.

HISTAMINE RECEPTOR ANTAGONISTS

Most studies evaluating first-generation, sedating type 1 histamine receptor antagonists were neither blinded nor randomized or controlled. They provide conflicting evidence of benefit for chlorpheniramine, clemastine, diphenhydramine, hydroxyzine, promethazine and trimeprazine for treatment of CAD. However, adverse effects are rare and consist most commonly of drowsiness. One blinded RCT provided *fair evidence of medium efficacy* of a combination of hydroxyzine (25–100 mg/dog/day) and chlorpheniramine (1–4 mg/kg/day). An improvement of more than 50% in lesional scores was seen in 18% and of pruritus scores in 30% of the dogs, investigators judged the treatment satisfactory in 24% of the dogs. This combination product is the first choice treatment with type 1 histamine receptor antagonists in our clinic.

Second-generation low-sedation type-1 histamine receptor antagonists such as loratidine and astemizole did not show efficacy in several studies, terfenadine showed conflicting results. Both terfinadine and astemizole can induce cardiac arrhythmias in dogs. Considering the concurrently demonstrated lack of efficacy, these antihistamines should be used cautiously for the therapy of CAD. Oxatomide at 1 to 2 mg/kg/day did show medium efficacy in several trials with 20% to 50% of patients exhibiting a satisfactory control of pruritus. Adverse effects were only mild and transient and consisted most commonly of increased appetite.

These trials provide *fair evidence of no or low efficacy* of the first-generation sedating type-1 histamine receptor antagonists chlorpheniramine, pheniramine, diphenhydramine, hydroxyzine, promethazine and trimeprazine for treatment of CAD, *fair evidence of* *medium efficacy* of treatment of canine AD with oxatomide and with a combination of chlorpheniramine and hydroxyzine. As a group, there is conflictual evidence of benefit of type-1 histamine receptor antagonists for treatment of canine AD.

POLYUNSATURATED FATTY ACIDS

There are a number of studies evaluating polyunsaturated fatty acids (PUFA) for the treatment of canine atopic dermatitis. Omega-6, omega 3 fatty acids or or a combination thereof were evaluated. In double-blinded, placebo-controlled studies, the difference between placebo and PUFA supplementation was typically significant, between 25% and 40% of patients responded favorably in the treatment groups. There is also evidence that concurrent administration of PUFAs decreases the requirements for glucocortocoids in atopic patients and that a combination of antihistamines and PUFAs is more effective than either therapy alone. Adverse effects of PUFA therapy were mild and typically consisted of diarrhea. There is *good evidence for moderate efficacy* of PUFA therapy in canine atopic dermatitis.

PHOSPODIESTERASE INHIBITORS

Papaverine, arophylline and pentoxifylline were all evaluated. Papaverine at 150 to 300 mg/dog twice daily did not lead to satisfactory control of pruritus in an open, nonblinded, non-randomised trial. In a randomized, controlled trial, arophylline at 1 mg/kg twice daily showed a fair efficacy with 50% reduction in lesional and 67% reduction in pruritus scores. However, vomiting was seen in 7/10 dogs and lethargy and polyuria in one dog each, 4 dogs treated with this drug did not complete the trial due to severe vomiting. Pentoxifylline at 10 mg/kg twice daily for 4 weeks was found to be more effective than placebo, it reduced erythema scores by 30% and pruritus scores by 35%. Clinical adverse effects were not noticed in this trial. Due to either inefficacy or an unacceptable rate of adverse effects, papaverine and arophylline cannot be recommended for the treatment of canine atopic dermatitis. There is *fair evidence for moderate efficacy* of pentoxifylline.

LEUKOTRIENE INHIBITORS

Leukotriene inhibitors have been evaluated for the treatment of canine atopic dermatitis in four trials, three of which were RCTs. Zafirlukast did show sustained fair to good reduction of pruritus in 2/18 dogs. Zileutin treatment did lead to a pruritus reduction of >50% in 3/9 (33%) of the dogs, erythema, but not pruritus scores were significantly lower that those of placebo treatment. In two other trials with leukotriene antagonists, no difference in lesion and pruritus scores between the drug and placebo was found. Zafirlukast caused vomition in two dogs, adverse effects were not seen with Zileutin. The trials provided *good evidence for no or very low efficacy* of leukotriene synthesis inhibitors or receptor antagonists for alleviation of clinical signs in dogs with CAD.

PROSTAGLANDIN ANALOGUES

A 4-week open study and a 3-week placebo-controlled blinded RCT evaluated the efficacy of treatment with the PGE_1 analog misoprostol. In both trials the clinician-assessed lesional scores and the owner-graded pruritus values were significantly lower at the end of the study compared to those at baseline. At the end of the RCT, and compared with subjects receiving placebo, dogs treated with misoprostol exhibited significantly higher percentage reduction from baseline of pruritus scores, but not of lesional values. Adverse drug effects were mild and intermittent and consisted of vomiting or diarrhea. These studies provide *fair evidence of medium efficacy* of the prostaglandin analog misoprostol (5 µg/kg three times daily for up to six weeks) to treat dogs with AD. Aspirin was evaluated in an open clinical trial of 45 dogs and achieved partial or complete remission of pruritus in only a small percentage of dogs. There is *limited evidence of no efficacy* of the prostaglandin inhibitor aspirin for treatment of this disease.

ALLERGEN-SPECIFIC IMMUNOTHERAPY

Although there are a number of studies evaluating the effect of ASIT on canine atopic dermatitis, most studies were retrospective and thus neither blinded nor controlled. In addition, in many studies follow-up times were short. Most of these studies report excellent efficacy in approximately 20% of the patients and good response in an additional 25% to 45%. The first prospective double-blinded, placebo-controlled study of ASIT in veterinary medicine reported 59% of 27 patients with significant improvement, but improvement was not evaluated with detailed clinical and pruritus scores used in more recent studies evaluating therapies for canine atopic dermatitis. Two years ago, a double-blinded RCT comparing conventional with rush immunotherapy found significant improvement in pruritus, medication and clinical scores after 12 months of immunotherapy, there was no significant improvement with conventional immunotherapy. As ASIT is a long-term therapy and many patients are in need of additional medication and as each patient has its unique set of allergens as well as possibly a unique protocol of administration to maximize success rate, scientific evaluation of ASIT is difficult. However, at this point, the numerous studies can be considered *fair evidence for moderate efficacy* of ASIT in the treatment of CAD.

TOPICAL ANTIPRURITIC DRUGS

An open four week trial evaluated two commercially available formulations of pramoxine-containing cream rinses. Overall, a good reduction (51% to 75%) in pruritus for 48 hours was assessed subjectively by the owners for seven dogs (41%). This provides *limited evidence of medium efficacy* of pramoxine. Another RCT compared the efficacy of whirl pool therapy with an antipruritic shampoo, conventional shampoo therapy and whirlpooling in water. Dogs improved significantly more with conventional shampooing and with shampoo therapy in the whirlpool compared to the control group, but there was no difference between the two modes of therapy. More dogs improved by 50% and 90%, respectively in the whirlpool group compared with the conventional shampoo treatment, but the difference was not statistically significant.

MISCELLANEOUS DRUGS

Taken together, three open studies provided *limited evidence of no efficacy* of the immune-modulating antibiotics erythromycin, doxycycline and tetracycline-niacinamide for pruritus reduction in dogs with canine AD. Of note is that such antibiotics could be considered for treatment of cutaneous bacterial infections that are often present during the course of canine AD. Three randomized trials provide *conflicting evidence of no or low efficacy* of the serotonin and histamine antagonist cyproheptadine. Administration of this drug commonly triggers an increase in appetite. Two open studies reported *limited evidence of variable efficacy* of the tricyclic antidepressants doxepin and amitriptyline. One trial provides *limited evidence of low efficacy* of Chinese herbal therapy. There is *limited evidence of no or low efficacy* of commercial homeopathic complex remedy, ascorbic acid, AHR-13268 and tranilast.

SUMMARY

Although there is a need for randomized controlled trials to evaluate many drugs currently used or under investigation for the treatment of canine atopic dermatitis, published studies allow some conclusions. Currently, there is good evidence for a high efficacy of glucocorticoids such as prednisolone or methylprednisolone at a dose of 0.5 to 1 mg/kg every 24 to 48 hours and cyclosporine at a dose of 5 mg/kg every 24 to 48 hours and a medium efficacy of polyunsaturated fatty acids and topical tacrolimus at 0.1% daily. Fair evidence can be provided for medium efficacy of allergen-specific immunotherapy, pentoxifylline at 10 to 15 mg/kg every 12 hours, misoprostol at 5 µg/kg q 8 hours, oxatomide at 1 to 2 mg/kg/day and a combination of chlorpheniramine and hydroxyzine at a dose of 1 to 4 and 25 to 100 mg/dog/day, respectively. For all other drugs evaluated there was either not enough evidence provided, no sufficient treatment success was found, or adverse effects were to severe to recommend them routinely for the treatment of canine atopic dermatitis.

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HOT TOPICS IN VETERINARY DERMATOLOGY

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ARE STORAGE MITE ALLERGENS RELEVANT?

Storage mite–specific immunoglobulin E (IgE) is frequently identified in dogs with atopic dermatitis. Similarly, atopic patients frequently show positive reactions to various storage mites on intradermal testing. The most commonly tested storage mites are *Acarus siro* (flour mite), *Tyrophagus putrescentiae* (mould mite), *Lepidoglyphus destructor* (hay mite), and *Glycyphagus domesticus*. However, it has been shown that normal dogs also react to storage mites, and that there is no difference in frequency of positive reactions between normal and atopic dogs. Similarly, it has been shown that cross-reactivity between dust mites and storage mites exists. Furthermore, two studies failed to identify storage mites in commercial dog food kept in normal households. So should we really include these storage mites antigens in allergen-specific immunotherapy extracts or should we categorically ignore the results of skin and serum testing regarding storage mites?

WHAT'S THE BEST WAY TO DO A HYPOALLERGENIC DIET TRIAL?

A diet trial is the best (actually, the only) way to diagnose food sensitivity in pets. There is no conclusive evidence that either a home-cooked diet, a commercial novel-protein diet, or a commercial hydrolyzed diet is better to use as a trial diet...use the one the pet will eat! The far more important factor is *client compliance* – that the client be VERY STRICT, which is nowadays much easier with the advent of a variety of hypoallergenic treats, snacks, and chews. Is table food permitted at all, like carrot sticks or fruit? Some authorities have recommended up to a 3-month trial period. Is this really necessary, or will a shorter period suffice? Also, is it permissible to concurrently use oral corticosteroids for the first couple of weeks of a hypoallergenic diet trial?

HOW DO I DEAL WITH RECURRENT PYODERMA IN A DOG WITH ATOPIC DERMATITIS?

Secondary bacterial infections, particularly with staphylococci, are common in dogs and humans with atopic dermatitis. Increased bacterial adhesion to corneocytes of atopic dogs and humans has been demonstrated, and clinical improvement of patients with secondary infections following oral antibiotic therapy as well as topical antimicrobial agents has been shown in a number of studies. However, chronic use of antimicrobial agents frequently meets owner resistance. Multi-drug resistant staphylococci are becoming a problem both in veterinary and human medicine, and resistant strains develop more easily with chronic use of antibiotics. Furthermore, in humans and dogs, individual patients with flaring infections may respond to aggressive anti-inflammatory therapy, without use of antibiotics. So, if a patient with chronic allergies is repeatedly presented with clinical and cytologic evidence of bacterial pyoderma, should we use antibiotic treatment long term, begin pulse therapy with antibiotics, or what other means should we consider?

WHY CAN'T I GET RID OF THIS DOG'S CHRONIC EAR DISEASE?

Recurrent or chronic otitis externa is a common and frustrating problem. One common reason why ear disease becomes recurrent is that multiple bacterial organisms are present in the infection, including multiple strains of difficult organisms such as *Pseudomonas*, and some of these are highly antibiotic resistant. A second reason is the presence of occlusive disease—narrowing or blockage in the ear canal by edema, hypertrophy, scarring, calcification, or masses. The presence of otitis media may also lead to lack of response to conservative treatment; this is difficult to assess without imaging procedures. Finally, bilateral chronic ear disease often occurs due to presence of an underlying inflammatory skin/ear disorder such as atopic dermatitis or primary seborrhea. Failure to consider each of these reasons for "chronic ears" will typically result in treatment failure.

HOW FAR DO I GO IN DIAGNOSTIC EVALUATION OF A DOG WITH ADULT-ONSED DEMODICOSIS?

Generalized demodicosis is a relatively common disease in veterinary dermatology. In young dogs, it is considered a genetically determined problem that allows abnormal proliferation of *Demodex* mites, a normal part of the cutaneous microfauna. In adult dogs, a suppressed immune system is often responsible. This may be reportedly due most commonly to administration of immunosuppressive drugs such as glucocorticoids, but hyperadrenocorticism, hypothyroidism and internal neoplasia have also been associated with adult onset demodicosis. In a dog with no history of drug administration and with no clinical signs of hormonal or neoplastic disease, a diagnostic workup for these diseases is indicated. How far should we go with such a workup? Is a biochemistry panel and complete blood count sufficient, should we proceed to determination of urine cortisol-creatinine ratios and thyroid hormone concentrations, possibly add ultrasounds, radiographs and lymph node aspirates or even routinely perform endocrine function testing and CT/MRI in these patients?

WHICH ALLERGY TEST IS THE BEST?

In the past, veterinary dermatologists have preached that serum-based "allergy tests" (allergen-specific IgE determinations) are unreliable, and that intradermal testing (IDT) is the only really reliable method for determining allergic sensitivities. Is this still true? Is referral for IDT still the best option, or should we consider use of the serum tests? Which serum test is the best? What are the important factors to consider when we use a serum allergy test?

SHAVE BIOPSIES OF THE PINNA – AN EASY AND COSMETICALLY APEALING TECHNIQUE

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Skin biopsy is a frequently used diagnostic procedure in veterinary dermatology. This is the diagnostic test of choice, particularly for immune-mediated and neoplastic disease. However, the punch biopsy, an easy technique on most parts of the body, is more difficult on the pinna. Similarly, wedge biopsies are not ideal on ears. Cartilage is found directly under a very thin dermis and the panniculus is absent on the pinnae. Punch and wedge biopsies lead to hemorrhage and suturing may lead to permanent change in the shape of the pinna. In addition, cartilage may inadvertently be damaged. Many diseases of the pinnae such as lupus erythematosus, diseases of the pemphigus complex, and infections with bacteria or yeast are diseases of the epidermis or dermo-epidermal junction. In these cases, deep biopsies showing panniculus, cartilage, or deep dermis are not necessarily needed. A shave biopsy is the technique of choice in these patients.

TECHNIQUE

This technique is to be performed under general anesthesia. However, as it is a fast procedure, inhalation anesthesia is not necessarily needed; injection anesthesia and analgesia will typically suffice. If the outside of the pinna is to be biopsied, it should be gently clipped with scissors. On the inside of the pinnae, clipping is usually not needed. A scalpel blade or shaving blade is held in one hand, the pinna is bent over the index finger of the other hand. On the stretched and bent convex surface, the scalpel blade is used to cut into the skin at an angle of approximately 20° until capillary bleeding is observed. At that particular depth the incision is continued parallel to the surface of the skin until a specimen of about 5 x 5 mm (0.25 x 0.25 inches) is obtained. This sliced-out specimen is a very thin piece of skin and needs to be placed with the dermal surface down on a piece of a tongue depressor or a cardboard. In addition, a piece of lens paper may be draped around the specimen and cardboard to ensure that the sample is not separated from the more easily visible base. Placing the thin specimen on a flat surface avoids distortion of the specimen in the formalin and at the same time ensures that the laboratory technician cutting in the biopsy will notice the small sample. The resulting ulceration on the surface of the pinna is dabbed with a silver nitrate stick to stop the hemorrhage. Alternatively pressure can be applied with a cotton swab for 2 to 5 minutes or electrocautery can be used. Suturing is not required and the lesions heal within a few days without any permanent damage. Histopathology will reveal changes of the epidermis and upper dermis, as the depth of the specimen with proper technique will reach the mid-follicular level. Changes on the surface of the skin, such as acantholytic cells in crusting (as seen in pemphigus) or bacterial or yeast colonies, epidermal changes such as intraepidermal pustules or vesicles or a possible interface dermatitis with basal cell vacuolization or apoptosis as seen in lupus may be appreciated. Thus, differentiation of pemphigus and superficial pyoderma from lupus erythematosus is typically possible. However, deep dermal changes such as vasculitis and pathology of the cartilage cannot be evaluated with this technique.

SUMMARY

Shave biopsies are a fast method of acquiring skin specimens to evaluate the epidermis and superficial dermis histologically and are particularly suited for areas of the body such as the pinnae, where suturing is difficult or may lead to permanent changes. They will reveal pathological changes in the epidermis and superficial dermis and are thus typically able to differentiate between infections and autoimmune diseases affecting the upper part of the skin such as pemphigus and lupus erythematosus. Healing of the sampling sites is usually without complications and permanent changes.

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CANINE ALOPECIA: WHAT'S NEW

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CANINE NON-INFLAMMATORY, NON-PRURITIC ALOPECIAS: DIFFERENTIAL DIAGNOSES

- **"Classic" endocrine alopecias** – Follicles telogenized, atrophic, hairless: hypothyroidism, hyperadrenocorticism, sex hormone imbalances (Sertoli's cell tumor, testicular neoplasia, cystic ovaries, ovarian neoplasia), pituitary dwarfism (growth hormone deficiency).
- **Hair cycle arrest syndromes** – Follicles in catagen or early telogen: Alopecia X (including adrenal sex hormone imblanace, castration responsive alopecia, sex hormone responsive dermatoses, maturity onset growth hormone responsive dermatosis), Siberian Husky follicular dysplasia (possibly), Malamute "Coat Funk" (possibly), post-clipping alopecia, telogen defluxion.
- **Follicular Dysplasia** – Abnormal follicular morphology: cyclic flank alopecia, color dilution alopecia , black hair follicular dysplasia
- **Crossover Syndromes** (hair cycle arrest and follicular dysplasia)? – Alopecias of the Irish Water Spaniel, Chesapeake Bay Retrievers, Portuguese Water Dog
- **Others** – Pattern baldness
- **Others** – Sebaceous adenitis (clinically non-inflammatory), alopecia areata (clinically non-inflammatory)
- **Congenital alopecia**

WHERE ARE WE NOW WITH RESPECT TO UTILIZING SKIN BIOPSIES TO BETTER DIFFERENTIATE THESE PROBLEMS?

Many of the above problems are diagnosed on the basis of history, physical examination (cyclic flank alopecia, pattern baldness), screening laboratory work including complete blood count (CBC), serum chemistry panel and urinalysis and more specific endocrinologic tests (hypothyroidism, hyperadrenocorticism) and/or response to trial therapy (eg, hypothyroidism, Sertoli's cell tumor). Biopsies are most commonly considered once hypothyroidism and hyperadrenocorticism have been ruled out as likely causes of alopecia.

Biopsies: Take samples from areas that are most significantly alopecic; ideally from the more dorsal areas of the thorax, abdomen, lumbar region (assuming affected) because the follicular units (follicles and adnexae are largest here and easiest for a pathologist to assess. In skin over the ventrum, the epidermis tends to be thinner than over the back and sebaceous glands tend to be smaller. These characteristics could mimic endocrine changes. A sample should also be taken from a more normally haired area.

One can mark the sample prior to taking the biopsy, which will allow for better visualization of the entire follicular unit from the epidermis to the deep dermis or subcutis. This is achieved by drawing a line (permanent marker; "sharp" Sharpie pen) along the lay of the hair and then centering the biopsy punch on this. Make it known to the pathologist that you have marked the sample and ask to have it cut in along the line.

CANINE ENDOCRINOPATHIES

Coat Changes Associated with "Classic" Endocrinopathies: Hypothyroidism, Hyperadrenocorticism (Spontaneous and Iatrogenic)

Failure of hair regrowth following clipping; irregular/abnormal shedding cycles; increased loss of hair; in some, may see retention of hair; lightening or "bleaching" of truncal coat color, with a tendency to spare the head and distal extremities (ie, the head and extremities retain their original color); changes in hair texture (coarse or frizzy hair); initial loss of hair over areas of wear (eg, dorsum of tail, axilla, inguinal area) with progression to a more classical bilaterally symmetric truncal alopecia that spares the head and distal extremities.

Skin changes: Cutaneous hyperpigmentation (earliest in areas of alopecia); comedones (most commonly over ventral abdomen); seborrhea (sicca or oleosa); skin thinning/atrophy (hyperadrenocorticism; often seen earliest in areas of previous scarring); skin thickening (hypothyroidism, associated with epidermal thickening and mucin deposition in the dermis). Patients with these endocrinopathies are often prone to recurrent/persistent bacterial pyoderma. These skin/coat changes are non-pruritic, unless complicated by secondary bacterial pyoderma or *Malassezia*. Secondary seborrhea may also potentiate pruritus, but it is usually mild. It is interesting to note that the cutaneous signs associated with hyperadrenocorticism may not all be related to just the overproduction of cortisol in affected individuals. It has been noted that adrenal sex hormones may also be produced in excess quantities in spontaneously Cushingoid patients. In one study of 10 dogs with PDH, elevated sex hormones were noted following ACTH stimulation with the following incidence: androstenedione (5 of 9), DHEAS (2 of 8), progesterone (6/10), 17 hydroxyprogesterone (4 of 10).

HAIR CYCLE ARREST SYNDROMES (PATHOGENESIS UNCLEAR)

Alopecia X (Hair Cycle Arrest)

Alopecia X is typified by hair follicles that are "arrested" in the catagen or telogen stage of the hair follicle cycle. For this reason, the syndrome has also been referred to as "Hair Cycle Arrest." It is most commonly seen in the Nordic breeds or "plush coated" breeds: chow chow, pomerainian, keeshound, samoyed, Siberian husky, Alaskan Malamute, American Eskimo dog and Finnish spitz. The miniature poodle also appears to be predisposed. Other individuals in other breeds may also be affected. Some have suggested that Malamute coat "funk," and follicular dysplasia of the Siberian husky may also fall within this category.

Affected dogs begin to develop hair loss as young, mature individuals, usually at 1 to 3 years of age.

However, older individuals may also develop the syndrome. Although the problem is more common in intact males, both males and females (intact or neutered) may be affected.

Alopecia is truncal, sparing the head and distal extremities. The truncal coat lightens in color, again sparing the head and distal extremities. There may be focal regrowth of hair at sites of trauma

The etiology of alopecia X remains very controversial. Affected individuals often do regrow hair following neutering or the administration of sex hormones, or the administration of sex hormone-altering drugs. Some, but not all affected dogs have been noted to have elevated basal and/or ACTH-stimulated progesterone, 17-hydroxyprogesterone, androstenedione, estradiol, or other sex hormone concentrations. This suggests an abnormality of adrenal sex hormone production. These hormones may have any one of a number of effects in the local metabolism of sex hormones at the follicular level, or on sex hormone receptors. Arguing against the importance of these sex hormones and sex hormone intermediates is the observation that successful treatment with either melatonin or mitotane does not alter sex hormone profiles in affected individuals. In some cases the sex hormone concentrations even worsen with trilostane therapy, in spite of hair re growth. In addition, after stimulating hair regrowth, hormonal therapy may be stopped in some and hair regrowth will continue to persist for many months to years. Spontaneous resolution of the problem has also been noted. It would seem more likely that this may be a primary hair growth disorder: a genetic predisposition to the development of a local defect in the hair growth cycle that may involve local follicular hormonal metabolism abnormalities and/or hormone receptor abnormalities.

The diagnosis is largely by history, physical findings, and rule out (ie, hypothyroidism, hyperadrenocorticism, etc.). Skin biopsies are suggestive, but not confirmatory. Hairs in most affected breeds tend to be in the early phase of telogen (so-called "flame follicles") with the "flame" description related to excessive tricholemmal keratinization. Sebaceous glands tend to be normal to slightly attenuated. In the Pomeranian, it has been noted that "flame" follicles do not tend to be as prominent, and instead, there may be more of a miniaturization of hair follicles. Pomeranians and non-Nordic breeds are also more likely to have dermal atrophy.

It is important to note that once alopecia X is strongly considered as the most likely diagnosis, no further workup may be necessary, especially if the owners are willing to live with an alopecic pet. To date, there are no obvious systemic abnormalities associated with this disease, and there is therefore no need to do further workup and therapy.

In the author's hands, diagnostics from this point are usually based on assessing response to therapy. Neutering is recommended initially. If this fails to be of benefit (or the patient must be left intact), we generally try melatonin for a 3-month period (3–6 mg BID to TID). We treat until maximal response is noted and discontinue the melatonin. Therapy is re instituted if and when signs recur. This protocol has been suggested to circumvent what some have noted as the development of an intolerance to the drug with chronic administration. Melatonin is noted to produce partial or complete coat regrowth in 50% to 60% of cases. Should this fail to be of benefit, we try methyltestosterone therapy (1 mg/kg to a maximum dose of 30 mg, once daily; generally tolerated well, but can cause hepatotoxicity, aggressive behavior and/or seborrhea; recommend a baseline liver profile prior to administration, then 1 and 2 months after initiating therapy). Supplementation is stopped after maximal regrowth is noted.

If melatonin or methyltestosterone fail to be of benefit, then we tend to recommend measuring sex hormones pre and post ACTH stimulation (eg, University of Tennessee sex hormone panel) If abnormalities are noted, there is rational for treating with mitotane (op,DDD; Lysodren) or trilostane.

Mitotane likely benefits affected individuals through its adrenolytic effect on the zona reticularis and fasiculata (from which sex hormones are produced). It may also have direct peripheral effects on follicle function. Induction is usually done at a more conservative dose of 15 to 25 mg/kg PO daily for 5 to 7 days. An ACTH stimulation is performed 24 hours after the induction dose is completed. The goal is to have the pre and post stimulation cortisols within the normal resting range for the laboratory being used (eg, pre and post cortisol should be 3 to 5 µg/dL). If cortisol values are as desired, the patient is placed on the daily induction dose (15–25 mg/kg) divided and given twice weekly. If the values are low, mitotane should be discontinued and started on a maintenance basis once cortisols have returned to the desired range. An ACTH stimulation test is generally performed 4 to 6 weeks after adequate induction, 3 months after this, then every 3 to 6 months thereafter. Consideration should be given to discontinuation of the mitotane therapy once full hair regrowth is noted (some will continue to grow hair for protracted periods of time). Success rates: in one study, 12 of 12 chows were noted to respond, in another study, 4 of 6 dogs were noted to respond.

Trilostane, a drug used to treat hyperadrenocorticism (competitive inhibitor of 13-beta-hydroxysteroid dehydrogenase, which interferes with adrenal steroidogenesis) promotes hair regrowth in non-Cushingoid individuals, but 17-hydroxyprogesterone concentrations consistently go up in treated individuals. Therapy is given daily until maximal regrowth is noted. At that time, consideration should be given to discontinuing the drug and assessing for duration of response (may be long term) or the need to establish a maintenance regimen (eg, two to three treatments weekly). In one study, response was noted in 13 of 16 Pomeranians and 8 of 8 miniature poodles. In another study, 3 of 3 Alaskan Malamutes responded to Trilostane therapy. Trilostane appears to be well tolerated but is expensive and must be ordered from abroad at present. A source (UK) and protocol for use and monitoring (cortisols are monitored by ACTH stimulation) is available at wwwmastermarketing.com.

FOLLICULAR DYSPLASIA

Canine Recurrent Flank Alopecia (Seasonal Flank Alopecia, Canine Idiopathic Cyclic Flank Alopecia, Cyclic Follicular Dysplasia)

These conditions hav a high incidence in Airedale terriers, Boxers, English bulldogs, Schnauzers, Griffon Korthals, Affenpinscher and Bearded Collie (genetic predisposition). Well-demarcated, variably symmetric alopecia and hyperpigmentation are noted over the flanks, lateral thoracoabdominal area, and may involve the dorsal and dorsolateral lumbar region. Episodes of alopecia are often recurrent (ie, hair loss in the fall, only to regrow in the spring or vice versa). The cycle may repeat itself yearly or skip years. It has been hypothesized that the problem may be related to a genetically influenced melatonin deficiency, which may affect the skin either directly or indirectly through melatonin's effects on prolactin, androgens, estrogens, and/or growth hormone. Melatonin can be used to shorten the duration of an alopecic episode or to prevent recurrence. Response to therapy is noted in about 50% to 75% of cases. Dosage is 3–6 mg given BID to TID for 2 months (until hair loss is not noted when expected as the season changes or until good hair regrowth is noted). Therapy is stopped once hair growth has been attained. Therapy is reinstitute for recurrences. A variant of this disease has been noted in the Golden retriever wherein cyclic alopecia is noted to develop over the bridge of the nose.

Color Dilution Alopecia

This condition is seen in the Blue Doberman, Great Dane, whippet, dachshund, standard poodle, chow chow, red and fawn Doberman, and fawn Irish setters. Born with a normal coat; gradually develop alopecia only affecting the color dilute (eg, blue) areas of the coat. In the past, treatments have been largely symptomatic (antiseborrheic shampoos, moisturizers; antibiotics for secondary infections). Oral synthetic retinoids (eg, isotretinoin, acetretin) have been suggested to produce some partial regrowth. More recently, melatonin has been noted to benefit some individuals (hair regrowth); dosage: 3–6 mg BID to TID until maximal response is noted. Response is noted in 30% to 40% of patients.

Follicular Dysplasias?

Other alopecic syndromes which have been thought to be follicular abnormalities +/- adrenal sex hormone abnormalities (perhaps similar to alopecia X in the Nordic breeds and miniature poodle) include alopecia of the Irish water spaniel, Chesapeake Bay retriever and Portuguese water dog. They often have abnormalities in sex hormone panels and histopathologic changes that suggest follicular dysplasia (clumped pigment in hair follicle and/or hair shaft). Although melatonin has not been reported to be effective in treating these individuals, the author has had some success with this drug in treating Chesapeake Bay retrievers with this problem.

OTHERS

Canine Pattern Alopecia (Pattern Baldness)

Signs include symmetrical hair loss behind the ears, ventral cervical, chest and abdomen, caudal thighs and perianally. It is seen primarily in the Dachshund, Boston Terrier, Chihuahua, Whippet, Italian Greyhound, greyhound, Boxer, and miniature pinschers. Individuals begin to lose hair about 6 months of age and gradually progress. Diagnosis by biopsy (follicles are both shorter and thinner than normal and residual hair shafts are extremely fine). Melatonin has been shown to be effective in regrowing hair in 50% to 70% of cases (1.5–6 mg/dog given BID or TID). Therapy is again used until good regrowth, then discontinued and reinstituted with recurrence of the problem.

Sebaceous Adenitis

An inflammatory destruction of the sebaceous glands accompanied by a defect in epidermal keratiniztion, the keratinization defect is seen as marked superficial and follicular hyperkeratosis. The cause is unknown. Studies done with the standard poodle suggest an autosomal recessive mode of inheritance in this breed.

A "focal form" of this disease is most commonly seen in the Visla and occasionally in other short-coated breeds. Affected dogs are presented with focal areas of alopecia and scaling. The skin is variably erythyematous. The head, back, and sides of the thorax and abdomen are most commonly affected. Diagnosis is by skin biopsy .This manifestation of the disease may, on occasion, be glucocorticoid responsive. Good to excellent responses have bee noted with retinoid therapy (isotretinoin, starting at 1–2 mg/kg/day) or oral cyclosporine therapy (5 mg/kg/day). Once complete remission has been achieved, some dogs will be able to have retinoid or cyclosporine therapy discontinued and will go in to indefinite remission. Others will require daily or every other day maintenance therapy to maintain remission. Topical therapy as outlined below for the generalized form of the disease may be tried, but it is usually not very effective.

The so called "generalized form" of the disease is most common and tends to affect longer haired breeds including the Standard Poodle, Samoyed and Akita and many other breeds (Old English Sheepdog, Toy Poodle, Lhasa Apso, Boxer, Chow Chow, German Shepherd dog and crosses, to mention just a few). Age of onset is usually 1 to 3 years, but the disease may develop in any aged individual. Hair loss is often focal and asymmetrical initially with progression to more symmetrical, generalized hair loss, and scaling. Primary areas of involvement include the head (including face), neck, back, sides of the thorax and abdomen, and anterior aspect of the extremities. The ventrum is usually less affected. Scale is heavy and adhered to the base of the hairs ("follicular casting"). The medial aspect of the pinna and canals are dry and scaly; there is often mild to moderate inflammation in the canals. Affected individuals may be prone to secondary staphylococcal pyoderma. Sebaceous adenitis is usually nonpruritic. The development of pruritus is usually attributed to the presence of secondary pyoderma or concurrent allergic disease.

Diagnosis is based on skin biopsy: there is usually moderate acanthosis and generally severe hyperkeratosis with follicular plugging. There is usually perifollicular inflammation localized in the region of the sebaceous glands. The severity of the inflammation varies from scant to severe (scant in chronic lesions). Sebaceous glands are absent.

There are several options for the treatment of this disease. With topical therapy, the overall goal is to remove scale. Following this there will usually be some hair regrowth, although the coat in general will usually not return to its original fullness. Systemic therapy, specifically with oral cyclosporine, has been noted to be associated with the return to most normal coats.

Option 1: Alpha Keri Bath Oil (or generic) is diluted 50:50 in water and applied over the entire coat/skin. It is left on for 1 to 3 hours, then removed with repeated shampooing (use a mild shampoo such as Ivory dishwater liquid; last shampoo or two can be with a veterinary sulfur/salicylic antiseborrheic shampoo). Repeat every 3 to 4 weeks until the scale is gone, then reduce frequency to maintenance. If not too labor intensive for the owners, ideally bathe with an anti seborrheic shampoo once weekly between oil baths. Ideally follow each of these antiseborrheic baths with a good conditioner (eg, Resi conditioner such as ResiSoothe; Allerderm/Virbac). Between more intensive oil therapies, propylene glycol (eg, Humilac) or propylene glycol (PG) diluted 50:50 with water can be sprayed on to the skin and left on once every day or other day. Some use this PG regimen instead of the more intense oil therapy: PG sprays daily; shampoo with antiseborrheic shampoo every 3 to 7 days initially; once scale is gone, start to decrease frequency of bathings first, then topical sprays. Long-term maintenance goal - Bath every 2 weeks, PG sprays 2 times per week. If desired, can use more concentrated propylene glycol spray. To reduce the need for more aggressive topical therapy patients are also treated with oral Vitamin A, 8,000 to 20,000 IU BID (50% show at least partial improvement) and fatty acids (Derm Caps (DVM) ES, 1 capsule BID; Evening Primrose oil, 500 mg BID).

Option 2: Oral tetracycline/niacinamide (500 mg of each/dog TID to initiate therapy) or tetracycline alone +/- topical therapies noted above.

Option 3: Cyclosprine (5 mg/kg q 24 hours orally) has been reported effective in dogs. Following the attainment of maximal response, the frequency or dose of cyclosporine is reduced. Topical cyclosporine (as a 1:10 dilution in water; used as a spray once daily to initiate therapy) has also been used effectively. Of all the therapies for sebaceous adenitis, cyclosporine appears to result in hair regrowth that is closest to normal. This therapy is also noted to potentially result in the regrowth of sebaceous glands.

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GERIATRÍA ¿PREVENIMOS O CURAMOS?

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La población geriátrica tanto de seres humanos como de perros y gatos se ha incrementado en los últimos años, debido al avance de la ciencia y a una alimentación más racional que permiten una mayor sobrevida.

Debemos tener en cuenta que casi el 40% de la población canina y felina que el médico veterinario atiende en su consultorio se encuentra en edad geriátrica.

Hay diversas hipótesis sobre que causa el envejecimiento y si bien ninguna lo explica por sí misma, la que ha tomado más importancia en los últimos tiempos es la acumulación en el organismo de residuos metabólicos como los radicales libres, responsables de la oxidación y destrucción de las membranas celulares.

Debido a esto último, la prevención, retardo o tratamiento de los síntomas de envejecimiento no pueden hacerse en base a una sola medicación.

Cuando el médico clínico se encuentra frente a un paciente geriátrico se encuentra con una multiplicidad de problemas que debe tener en cuenta, puede que el cuadro predominante sea osteoarticular, ocular, dérmico, renal, etc., o lo más común que sea una mezcla de todas esas patologías. Frente a este panorama tenemos dos alternativas, tratamos al paciente con la vista puesta en la enfermedad predominante o lo vemos como una integridad y le suministramos un tratamiento que apunte a mejorar al animal integralmente.

Sabemos que los animales domésticos envejecen de manera diferente de acuerdo a tamaño, peso y raza del animal.

Los animales de mayor tamaño envejecen con más rapidez que los más pequeños, los más gordos que los más delgados y los de raza más rápido que los mestizos.

A modo de ejemplo la siguiente tabla nos muestra los años promedio de vida en razas grandes comparada con las de menor peso y tamaño.

Debemos tener en cuenta que en la vida de una mascota hay dos momentos en que el propietario le presta mayor atención, la primera es cuando lo compra, es decir, de cachorro y el segundo momento es cuando envejece y el vínculo con el animal se hace más fuerte.

Cuando es cachorro los clínicos implementamos un plan de prevención que emplea vacunas, desparasitaciones y medidas higiénicas de todo tipo para evitar la enfermedad.

El propósito de esta presentación es que tratemos de hacer lo mismo en el otro extremo de la vida del animal.

Como se dice al principio la teoría que mayor importancia ha tomado en la explicación del envejecimiento es la acumulación de radicales libres. Los mismos actúan en diferentes lugares de la célula, como los fosfolípidos de las membranas o en las mitocondrias y cuando el equilibrio entre radicales libres y mecanismos antioxidantes se vuelca a favor de los primeros se produce el estrés oxidativo y la posterior muerte celular.

Veamos como ocurre este proceso. El organismo posee sistemas enzimáticos endógenos para la prevención del mismo que funcionan desde el comienzo de la vida, ellos son la superóxido dismutasa (SOD), la glutatión peroxidasa (GSH-Px) y la catalasa (CAT), los mismos se ponen en marcha ante la acumulación de

Estimación de la edad media de perros y gatos Geriátricos

Perros de razas pequeñas (0-10 kg) = 11,4 años +/- 1,8 años

Perros de razas medianas (10-25 kg) = 10.9 +/- 1,5 años

Perros de razas grandes (25-45 kg) = 8,8 +/- 1,3 años

Perros de razas gigantes (>45 kg) = 7,4 +/- 1,9 años

Gatos = 11,8+/- 1,9 años

Goldston - 1989

radicales libres y necesitan para un correcto trabajo la presencia de elementos como el cobre, zinc y manganeso en el caso de la superóxido dismutasa y de selenio en el caso de la glutatión peróxidasa.

Pero eso no alcanza, el organismo para mantener un equilibrio favorable, requiere la incorporación de antioxidantes con la dieta, ejemplo de ellos son las vitaminas E y C, la taurina y los carotenoides.

Cuando estos mecanismos tanto endógenos como exógenos se resienten el predominio de los radicales libres lleva al estrés oxidativo al actuar sobre el ADN celular, produciendo , alteración en la expresión del gen, destrucción de los mecanismos de reparación tisular y distorsión de la función celular.

Todo esto ocasiona la muerte celular, que a su vez produce la aparición de enfermedades relacionadas con el envejecimiento, así tendremos un organismo con enfermedad cardiovascular, respuesta inmunitaria baja, disfunción cognoscitiva y tantas otras patologías.

Ya se dijo que al tratar un geronte estamos tratando varias patologías simultáneamente. ¿Qué hacer entonces?

El clínico debe implementar un plan para cuidar mejor al animal añoso.

Debemos tener en cuenta que un animal a partir de los siete u ocho años requiere cuidados especiales, por lo tanto la atención en consultorio deberá poner en práctica entre otras cosas análisis clínicos, mayor frecuencia de visitas y educación al propietario sobre los síntomas a tener en cuenta.

Los propietarios en general aceptan las sugerencias del médico veterinario, pues debemos tener en cuenta que en muchos casos al animal se lo atiende desde su nacimiento. Si logramos que el dueño de la mascota entienda la importancia de un plan de prevención de la vejez, evitaremos tener que atender pacientes que llegan al consultorio en un estadío final y con pocas posibilidades de solución. Por otra parte habremos logrado fortalecer la relación médico veterinario – dueño de la mascota y obtener un beneficio compartido, pues al propio beneficio económico que esto conlleva, se debe sumar el beneficio de satisfacción del propietario y lo más importante retrasar los síntomas de envejecimiento y mejorar la calidad de vida de nuestro paciente en esta etapa.

¿EL ENVEJECIMIENTO, SE PUEDE DIAGNOSTICAR?

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El envejecimiento es un proceso gradual, progresivo y al mismo tiempo irreversible, por lo tanto, la teoría de la juventud eterna por el momento debemos descartarla.

De todas formas en este camino hacia la senilidad no siempre la edad biológica es coincidente con la cronológica, es decir que un animal de doce años que cronológicamente es un animal senil puede biológicamente estar mejor que uno de ocho años.

Está probado que los animales envejecen de diferente forma de acuerdo al tamaño, peso, raza, etc. Los animales de mayor porte como un Gran Danés, comienzan su proceso de envejecimiento entre los seis y siete años mientras que un Yorkshire Terrier es probable que presente síntomas seniles recién a los diez u once años.

A estas diferencias raciales y genéticas tienen que sumarse otras, como diferentes condiciones ambientales, tipo de alimentación, cuidados a lo largo de la vida, que hacen que un animal pueda deteriorarse más rápido que otro.

El envejecimiento lleva como consecuencia final a la muerte del animal, en aquellos que mueren tempranamente la misma en general está asociada con alguna enfermedad subyacente grave.

Entonces, como conclusión, podemos decir que los cambios del envejecimiento son progresivos e irreversibles y tienen que ver con una combinación de factores como las enfermedades, el estrés, la nutrición, los factores genéticos, el medio ambiente y el ejercicio.

A pesar de ello no podemos afirmar que la vejez es sinónimo de mala salud, en algunos animales esto se puede dar simultáneamente pero no siempre es así.

Dice el Doctor Johnny D. Hoskins en su libro sobre Geriatría y Gerontología del perro y el gato “la prevención, la detección temprana y la intervención oportuna en los problemas médicos pueden ejercer un impacto significativo sobre la supervivencia y la calidad de vida de un perro o gato de edad avanzada”.

Los clínicos veterinarios deben tener en cuenta qué hacer con el propietario de una mascota que llega a los siete u ocho años de edad. Esta es una tarea docente basada en enseñarle al dueño básicamente dos cosas, la primera estar atento a síntomas clínicos que son fáciles de ver y que en general pasan desapercibidos o no se les da importancia.

El segundo punto sobre el que debemos instruir al dueño de la mascota senil es en la necesidad de controles periódicos para poder adelantar nuestro diagnóstico y así utilizar los recursos terapéuticos necesarios para demorar todo lo posible los síntomas clínicos de enfermedad.

Para comenzar podríamos hacer un listado que debería comprender entre otros los siguientes:

- Problemas locomotores simples como dificultad en subirse a un sillón, cama, al auto, etc.
- Aumento en la ingesta de líquido y emisión de orina (polidipsia y poliuria)
- Trastornos en la visión.
- Olor en la piel.
- Aumento en la caída de pelo
- Cambios de hábitos higiénicos, sobre todo en los felinos que viven en departamentos y tienen lugares fijos para sus deposiciones y micciones.
- Cambios de conducta, ya sea, que estos viren a la agresividad o pasividad del animal.
- Dificultad en adaptarse a situaciones nuevas y al reconocimiento de personas con las cuales ha convivido el animal durante años.

Este listado que podría comprender varios puntos más, debería ser provisto al propietario de una mascota para que nos ayude en el diagnóstico precoz del envejecimiento. La rapidez en la detección de estos síntomas, que muchos entenderán como síntomas subjetivos, y es cierto que lo son, nos permitirán adelantarnos a síntomas más objetivos pero también más graves.

El veterinario clínico no debe esperar a tener frente a él un animal con parálisis o paresia del tren posterior, o con una insuficiencia renal para comenzar un tratamiento.

Así como en el cachorro implementa un plan de vacunación, desparasita y toma los recaudos para realizar un plan sanitario que permita al animal crecer y desarrollarse sin enfermedades; en el otro extremo de la vida, que es la vejez, debe buscar recursos para adelantarse a la aparición de síntomas. De esa manera, no evitará la presentación de enfermedades graves que seguramente llegarán, sino logrará retrasar la aparición de sus síntomas y dará mejor calidad de vida a la mascota en tratamiento.

Además de estos síntomas subjetivos que pueden ser motivo de discusión hay otros que podemos objetivar.

El tercer punto sobre el que se debe instruir al dueño de la mascota senil es la necesidad de controles periódicos para poder adelantar el diagnóstico y poner en práctica los recursos terapéuticos necesarios para demorar todo lo posible síntomas graves de enfermedad.

Hay trabajos realizados donde se observó y analizó la correlación entre parámetros sanguíneos y la edad y donde se concluye, que con el paso de los años, algunos de ellos aumentan y otros disminuyen.

Entre los valores que tienden a aumentar se encuentran los siguientes: urea, fósforo inorgánico, glucosa, potasio, volumen corpuscular medio, leucocitos totales, neutrófilos y eosinófilos. Los que disminuyen son: calcio, linfocitos y eritrograma.

El clínico veterinario tiene a su disposición valores hemáticos de referencia para animales jóvenes y adultos, pero carece todavía de suficientes estudios poblacionales para estandarizar "valores fisiológicos" en el animal geronte.

De todas formas es real que un aumento por encima de los valores fisiológicos en un animal de más de siete u ocho años está señalando que algo pasa. Para poner un ejemplo que se entienda: si llega un paciente de esta edad con una uremia de 50 o 60 mg/dl, no se puede asegurar que el animal tenga una insuficiencia renal, pero se debe pensar que ese riñón seguramente tiene un daño en un número importante de nefrones que seguramente disminuye la filtración glomerular. Lo mismo estará pasando en otros órganos que van lentamente deteriorando sus funciones y modificando gradualmente los valores sanguíneos.

Es aquí donde cobra importancia la implementación de controles periódicos al gerente, dentro de un plan integral de salud que permita al clínico realizar un diagnóstico precoz y no esperar a tener uremias de 300 o 400 mg/dl frente a las cuales probablemente sea poco lo que se puede hacer.

La puesta en práctica de este tipo de controles que podemos llamar "perfil geriátrico", busca tener un diagnóstico de envejecimiento y al mismo tiempo parámetros cuantificables y así poder seguir la evolución del proceso y la respuesta al tratamiento establecido.

Si se comienza a implementar este método seguramente se logrará retrasar la aparición de síntomas más graves y mejorar la calidad de vida del animal geronte.

ENFERMEDADES OSTEOARTICULARES: UN PROBLEMA DEL GERONTE

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El incremento que ha sufrido el promedio de vida de nuestras mascotas, debido a una mejor atención médica, una mejor alimentación y un mayor contacto con el ser humano aumentó el porcentaje de animales gerontes que el médico veterinario diariamente debe atender en su consultorio.

Dentro de las patologías más comunes que pueden observarse están, sin ninguna duda, las enfermedades músculoesqueléticas. Estas se pueden presentar como enfermedad única o en combinación con patologías renales, cardíacas, etc.

Sin duda, la enfermedad músculoesquelética por excelencia es la enfermedad articular degenerativa. Se caracteriza por un cambio degenerativo en el cartílago articular y tiene, una forma primaria, cuando lo que produce ese cambio es sólo el envejecimiento, o una forma secundaria, que aparece cuando hay una enfermedad previa, como la displasia de cadera o una osteocondritis disecante ó una causa traumática como la ruptura de ligamentos cruzados.

Es importante cuando se encara el diagnóstico de esta enfermedad tratar de ver al paciente como una integridad y no sólo como una rodilla o cualquier otra articulación enferma.

Las enfermedades osteoarticulares requieren un tratamiento que considere no sólo la patología puntual sino una visión general del paciente. Para dar un ejemplo: si vamos a tratar una enfermedad articular degenerativa primaria en un perro obeso, lo primero que debemos hacer es ponerlo a dieta y que baje de peso, de lo contrario los tratamientos a implementar tendrán destino de fracaso.

Con el correr de los años hay cambios degenerativos en el cartílago articular, los cuales modifican la histología y la bioquímica articular.

Veamos los constituyentes normales de una articulación y como se produce el deterioro que lleva a la enfermedad, para después poder instaurar el mejor tratamiento posible.

Articulación: Componentes

- Hueso Subcondral
- Cartílago
    - Células: Condrocito
    - Matriz extracelular: Fibras Sustancia básica (mucopolisacáridos)
- Membrana sinovial
- Cápsula articular–Ligamentos intra y extrarticulares
- Líquido sinovial

Siguiendo el cuadro debemos considerar en primer lugar al hueso subcondral que da soporte a la articulación, siendo el último receptor de las presiones articulares. Tiene una estructura esponjosa que protege al cartílago del daño traumático. El endurecimiento del hueso subcondral que ocurre en la artritis puede llevar a la muerte del cartílago, está muy inervado e irrigado.

El cartílago articular normal es denso, blanco y brillante, con el tiempo adquiere una coloración amarillenta. La superficie del mismo no es plana, tiene pequeñas depresiones irregulares correspondientes a la localización de los condorcitos por debajo de la superficie articular. Carece de inervación e irrigación y su composición es básicamente un 70% de agua y un 30% de colágeno y proteoglicanos.

El condrocito es el único elemento vivo del cartílago y por lo tanto, es el único que elabora los componentes del mismo, de allí la importancia de mantener el equilibrio entre el anabolismo y catabolismo del mismo, para asegurar el normal funcionamiento del cartílago.

El condrocito produce fibras colágenas, elásticas y mucopoliscáridos,entre estos últimos encontramos a los proteoglicanos y al ácido hialurónico. Los proteoglicanos forman la base de sustentación de los GAGS, dan soporte a las células, resisten la compresión y forman filtros moleculares, retrasando el movimiento de microorganismos y células metastásicas. El ácido hialurónico producido por el condrocito, se une con los proteoglicanos formando una macromolécula de mucopolisacáridos, de esta manera,
participa dando resistencia a la compresión del cartílago.

En resumen el cartílago articular no tiene inervación , ni irrigación y se nutre por difusión a partir de los vasos sanguíneos de la membrana sinovial. La difusión se realiza a través del agua.

La membrana sinovial contribuye a la estabilidad articular, produce líquido sinovial y transporta nutrientes hacia la articulación y residuos metabólicos fuera de la misma .

En cuanto a la cápsula articular incluye una cantidad significativa de tejido que permite un amplio movimiento articular, pero a la vez actúa como estabilizador de la articulación, en particular si es tensionada en los extremos de flexión o extensión.

Por último, el líquido sinovial es un dializado sanguíneo originado en los plexos de la capa de sostén de la membrana sinovial. Es un líquido viscoso, transparente e incoloro. Las articulaciones normales contienen sólo un volumen reducido del mismo. Podemos decir que el líquido sinovial es plasma más ácido hialurónico y que actúa en la lubricación de tejidos blandos y del cartílago articular, evitando la migración leucocitaria y disminuyendo la síntesis de PGE_3.

¿Cómo llegamos a la enfermedad? La enfermedad osteoarticular se define como la pérdida del cartílago articular y muerte de los condrocitos.

Para ser más específicos digamos que la enfermedad articular degenerativa es una enfermedad progresiva compleja que puede definirse de varios modos. En términos patológicos "es un desorden intrínsecamente no inflamatorio de las articulaciones móviles (sinoviales) caracterizado por el deterioro del cartílago articular y la neoformación ósea en las superficies y márgenes articulares".

Desde el punto de vista clínico es "una enfermedad articular de evolución lenta caracterizada por el desarrollo gradual de dolor, rigidez y restricción del movimiento articular".

Esta enfermedad tiene una etiología multifactorial donde intervienen factores genéticos, metabólicos, biomecánicos, etc.

La causa última en su aparición se debe al desequilibrio entre el desgaste permanente al que está sometido el cartílago articular, frente a la limitada capacidad regeneradora de este tejido.

La fisiopatología nos muestra una disminución del anabolismo, pues el condorcito disminuye la producción de proteoglicanos, colágeno tipo II, agua y ácido hialurónico y al mismo tiempo hay un aumento del catabolismo representado por la presencia de enzimas proteolíticas como las colagenasas que terminan produciendo la muerte del condrocito.

Esto afecta también a la membrana y al líquido sinovial, en la primera se inicia el proceso inflamatorio y el segundo cambia su composición y apariencia, disminuída entonces la capacidad de amortiguación, se fisura el cartílago articular y aparece el dolor. También el hueso subcondral comienza a sufrir impactos, se esclerosa, se producen micro fracturas y todo esto lleva a la formación de osteofitos.

Frente a este cuadro el objetivo del tratamiento será recuperar la función articular, tratando de inhibir la inflamación, aliviar el dolor, regenerar las superficies articulares, recuperar el cartílago y reparar el hueso subcondral.

El tratamiento puede ser encarado con antiinflamatorios no esteroides (AINES), antiinflamatorios esteroides, condroprotectores o regeneradores osteoarticulares o en algunos casos una combinación de ellos.

Pero lo más importante en este caso es tener en cuenta al paciente como una integridad, tener en cuenta que estamos frente a un paciente geronte que seguramente además de la patología articular, tiene daños en otros órganos del cuerpo, que este tratamiento se prolonga en el tiempo y que lo que debemos hacer es causar el menor daño posible, tratando de minimizar los efectos colaterales del mismo.

De los tratamientos antes mencionados los que reúnen estas condiciones, o sea, poder ser utilizados por largo tiempo y con el menor efecto colateral, están los condroprotectores como la glucosamina y el condroitín sulfato y los regeneradores articulares que agregan a los anteriores, aminoácidos, minerales como el cobre, zinc, magnesio y manganeso, vitaminas como la E y el grupo B que permiten un tratamiento sin complicaciones secundarias.

Es importante complementar estos tratamientos con otras medidas terapéuticas como la fisioterapia y la rehabilitación y la instrucción al propietario en el manejo del animal, indicando en caso de ser necesario, dietas, ejercicios moderados, aplicación de calor seco en las zonas afectadas o cualquier otra medida que ayude a la recuperación fisiológica del paciente.

DIAGNÓSTICO DE DISFUNCIÓN COGNOSCITIVA

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Entre las enfermedades comunes del animal geronte se encuentran distintas manifestaciones de la conducta que en muchas oportunidades no son advertidas por el propietario y que deben figurar como síntomas de alerta en los planes de atención geriátrica de los diferentes centros hospitalarios.

El proceso de envejecimiento es lento e irreversible y en él se manifiesta un deterioro de la función cognoscitiva como la pérdida de memoria, la falta de percepción, el olvido de las conductas aprendidas y también de la conciencia.

Estos cuatro enunciados generales tienen un correlato con síntomas concretos que observa el propietario y el clínico en la práctica diaria.

Los animales con deterioro cognoscitivo no se ubican en tiempo y espacio, aún dentro de su propio hogar, pueden desconocer a quienes viven con ellos, volverse agresivos con las personas o con otros animales, pierden los hábitos aprendidos, como los de higiene y pueden comenzar a evacuar dentro del hogar.

Son muchos los síntomas que pueden poner de manifiesto el deterioro cognoscitivo y es muy importante que el clínico pueda diferenciar éstos, de una manifestación de enfermedad.

Para ello es importante realizar pruebas de laboratorio que nos permitan descartar la enfermedad; hemograma y perfil bioquímico, hepatograma, análisis de orina, radiografía, ecografía, electro o ecocardiograma o cualquier otra prueba que el médico veterinario necesite para el diagnóstico diferencial, debe ser usada.

Una vez descartada la causa orgánica, debemos analizar que ocurre en el ambiente. En muchas oportunidades la llegada de un bebé al hogar, un divorcio, la presencia de otra mascota, etc., pueden alterar la conducta del animal sin que esto sea un síntoma de disfunción cognoscitiva.

Como se ve no es fácil llegar a un diagnóstico certero y en ese sentido debemos tener en cuenta que el animal geronte difícilmente presente un solo problema. Lo más común es que sea una combinación de patologías.

Es probable que un perro de diez años con cataratas, tenga además de la dificultad visual, una artrosis y si es un macho, algún problema prostático. Entonces será difícil de evaluar, cuando el animal se torna agresivo al acercarnos, si lo hace porque tiene dolor por la artrosis, si no nos reconoce porque no nos ve o si esto es causa del deterioro cerebral por la edad.

Como otro ejemplo de lo dicho, los problemas osteoarticulares provocan dolor, disminución de la masa muscular y dificultad en el movimiento, estos procesos son crónicos, por lo tanto, el malestar que siente el animal también lo será y probablemente el dolor y la falta de movilidad hagan que el animal no pueda llegar a los sitios de evacuación habituales.

Es muy importante por lo tanto, poder diferenciar los cambios de conducta secundarios a distintas patologías, de los cambios de conducta producto del deterioro cerebral.

Debemos tener presente que los cambios degenerativos cerebrales tienen como consecuencia la disfunción cognoscitiva.

En un geronte se produce un achicamiento de la masa cerebral, hay reducción del número de neuronas, desmielinización y degeneración neuroaxonal. También cambios vasculares y perivasculares que incluyen la hemorragia y los infartos.

Cada día hay más pruebas sobre la responsabilidad que la acumulación del amiloide beta tiene en el desarrollo de la disfunción cognoscitiva, el mismo no se halla en perros jóvenes, pero sí en perros de edad y a mayor acumulación de amiloide, hay un mayor deterioro cognoscitivo.

La acumulación de amiloide beta, trae alteraciones funcionales en los neurotrasmisores, arterioesclerosis no lipídica, placas del mismo en cerebro e hipocampo, insuficiencia vascular, declinación de la actividad colinérgica y mayor producción de radicales libres.

El resultado de esta acumulación y la zona afectada por la misma, será el corolario para la presentación de síntomas clínicos que nos permitirán hacer el diagnóstico de disfunción cognoscitiva.

Finalmente, se presenta una tabla orientativa con los síntomas más comunes de la disfunción cognoscitiva en perros y gatos.

Perros	**Gatos**
Ansiedad por separación	Eliminación en lugares inapropiados
Agresión a personas	Agresión hacia animales de la misma especie
Agresión a animales	Agresión a personas
Trastornos compulsivos	Vocalización excesiva
Fobias	Deambulación nocturna
Ansiedad	Acicalamiento excesivo
Evacuación en el hogar	Miedo
Aumento de vocalización	Arañazos

TRATAMIENTO DE DISFUNCIÓN COGNOSCITIVA

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Definimos a la disfunción cognoscitiva como los problemas de conducta causados por los efectos de procesos neurodegenerativos cerebrales.

Siguiendo la definición podemos afirmar que no todos los animales que envejecen sufren disfunción cognoscitiva Esto quiere decir que no es una consecuencia inevitable del envejecimiento y por lo tanto debemos tener la certeza del diagnóstico para poder implementar el tratamiento.

Los cambios que se producen en un cerebro senil abarcan varios aspectos, hay una actividad incrementada de la monoaminooxidasa B (MAOB), disminución en la función de los neurotrasmisores como la noradrenalina, serotonina y dopamina, declinación de la actividad colinérgica y un incremento en la producción de radicales libres.

Otro factor que puede influir, es la insuficiencia vascular, la que podría potenciar el proceso neurodegenerativo al producir hipoxia cerebral.

La falta de oxígeno actúa a nivel de la mitocondria y a medida que ésta envejece produce una mayor cantidad de radicales libres, en caso que la producción de los mismos sea mayor que la capacidad del organismo para poner en acción sus defensas antioxidantes, se produce un proceso llamado estrés oxidativo que termina en la muerte celular.

El cerebro sufre especialmente los efectos adversos que trae la acumulación de radicales libres ya que es un tejido con alta demanda de oxígeno, alto contenido en lípidos y tiene dificultad para poner en marcha los mecanismos antioxidantes y de reparación de sus tejidos.

El tratamiento de la disfunción cognoscitiva debe entonces contemplar dos aspectos, debe hacerse un tratamiento que podemos llamar higiénico o nutricional y otro medicamentoso.

El primero de ellos tiende a aportar al animal un ambiente favorable y cuidados especiales, como ejercicios programados, paseos y otras actividades que mantengan atento al animal.

Además, se debe proveer una dieta rica en antioxidantes que permita contrarrestar el efecto que produce la acumulación de radicales libres.

Es importante suministrar vitamina E y C, ya que la primera protege a las membranas celulares depurando los radicales libres e interrumpiendo la peroxidación de los lípidos y la segunda tiene un papel muy importante como antioxidante, y además ayuda a regenerar a la vitamina E.

También debemos incorporar omega 3 que tiene efectos beneficiosos sobre la circulación sanguínea (microcirculación) fluidificando la sangre al evitar la formación de trombos, asimismo actúa como antioxidante y favorece la formación de mielina.

Por último no deben faltar en la dieta carotenoides y l-carnitina, ya que esta última actúa mejorando la función mitocondrial.

En cuanto al tratamiento médico, el de elección es con selegilina. El clorhidrato de selegilina habitualmente denominado l-deprenil, está indicado en la disfunción cognoscitiva y en el tratamiento del síndrome de Cushing, aunque en este último caso, su uso es controvertido.

En el humano se usa como tratamiento adyuvante de la enfermedad de Parkinson.

La selegilina actúa inhibiendo la monoaminooxidasa, esto produce un aumento en los receptores de dopamina y de otras catecolaminas en la corteza e hipocampo.

También contribuye a disminuir la carga de radicales libres, pues al inhibir a la monoaminooxidasa depura en forma directa a los radicales libres y aumenta el nivel de enzimas depuradoras como catalasa y superóxido dismutasa.

Entre los efectos adversos se incluyen el vómito, la diarrea y efectos nerviosos centrales, como inquietud, movimientos repetitivos o letargia, salivación y anorexia.

De todas formas la experiencia clínica con esta droga es limitada y podría modificarse el perfil de estos efectos colaterales.

La dosis indicada es de 0,5 a 1 miligramo por vía oral, una vez al día, de preferencia por la mañana. Los ajustes de esta dosis se harán de acuerdo a respuesta y tolerancia a la droga.

Entre otros tratamientos que pueden ser utilizados están los siguientes:

- La nicergolina, que es un antagonista α_1 y α_2 – adrenérgico, la dosis recomendada es de 0,25 a 0,5 miligramos/ kilo/ día.
- El clorhidrato de nilidrina, un agonista β – adrenérgico, es un vasodilatador y se dosifica de 3 a 6 miligramos, tres veces al día/ total.
- Por último la propentofilina, aumenta el suministro de oxígeno al sistema nervioso central y se recomiendo una dosis de 3 miligramos/ kilo/ cada 8 horas.

Es importante recordar que el éxito de un tratamiento dependerá no sólo de la utilización de la droga adecuada sino también de la implementación de una nutrición y régimen de actividad acorde a la patología a tratar.

COMO SÉ SI MI PACIENTE TIENE CÁNCER?

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Los siguientes signos clícios frecuentemente esan asociados co un diagnóstico de cancer: presencia de un bulto o masa, pérdida de peso, vómitos/diarrea, poliuria/polidipsia (eg; hipercalcemia), hemorragias de orificios naturals, etc. Sin embargo, también pueden deberse a una gran variedad de problemas medicos o quirúrgicos no neoplásicos.

Después de obtener una Buena anamnesis y hacer una exploración clínica, habitualmente el clínico identifica una masa o lesión inflitrativa en este paciente. Cómo determinamos si es una lesion neoplásica o no? El primer paso: CITOLOGIA.

Los especimenes para evaluación citológica son fáciles de obtener. Además, la obtención de la muestra habitualmente no requiere anestesia local o general, los resultados son rápidos, y el porcentaje de complicaciones es extremadamente bajo.

La mayoría de los tejidos pueden ser evaluados a través de citología, incluyendo lesiones de piel, ganglios linfáticos superficiales y profundos, órganos parenquimatosos, lesiones pulmonares intersticiales o metastáticas, y efusiones en cavidades corporales. En general, para hacer una punción se utiliza una aguja fina (calibre 22, 23, ó 25 G), ya que una aguja de diámetro más grande habitualmente obtiene un pequeño "tapón" de tejido, con el cual es muy difícil hacer extendidos.

OBTENCIÓN DE MUESTRAS

Existen varias técnicas para obtener muestras para citología. Una vez que se ha obtenido la muestra, los frotis son procesados en forma similar.

Aspiracion por Aguja Fina (Puncion)

Usando esta técnica, es posible obtener una suspension monocelular a través de una aguja fina (calibre 22, 23, ó 25G) acoplada a una jeringa de 12 a 20 ml (o no). Es muy fácil aspirar masas de piel o tejido subcutáneo, ganglios superficiales o profundos, bazo, hígado, riñones, pulmones, tiroides, próstata, y tumores intracavitarios (eg; masas mediastínicas).

Cuando se punza un tumor superficial o un ganglio, no hace falta preparar el área en forma estéril. Sin embrago, cuando se aspira una masa u órgano intracavitario, es preferible afeitar y esterilizar la zona. Una vez que la masa ha sido identificada a través de palpación, radiografías, o ultrasonido, se la debe "fijar" por medio de la palpación. Inmediatamente se inserta una aguja (acoplada a una jeringa descartable o no) en la masa/órgano afectado; si no se usa jeringa, punzamos la masa varias veces insertando y sacando la aguja. Una vez retirada la aguja de la masa, se pone aire en una jeringa y se expele el contenido en portaobjetos (laminillas) como se decribe más abajo. Si se usa jeringa, se aplica succión con el émbolo 3 ó 4 veces. Se debe interrumpir la succión antes de retirar la aguja de la masa/órgano, ya que de no ser así, las células se van a aspirar dentro de la jeringa, donde no son accesibles. Una vez removidas la aguja y jeringa juntas, se separa la aguja de la jeringa, y una vez aspirado aire dentro de la jeringa, la aguja se vueleve a acoplar, y el material se expele en varios portaobjetos. En la mayoría de los casos, no hay material en la jeringa, ya que la cantidad de células contenidas en la aguja son suficientes para hacer de 4 a 10 frotis. En la clínica hacemos frotis "de tirado" en vez de hacer los frotis hematológicos tradicionales. Una vez hechos los frotis, se secan al aire y se colorean con Diff-Quik, Giemsa, o May-Grunwald.

Liquidos de Puncion

Después de obtener líquidos de punción, es preferible preservar las muestras en tubos con y sin anticoagulante, ya que el alto contenido de fibrinógeno de algunos liquidos hace que coagulen rapidamente. Además de hacer una evaluación bioquímica del líquido, es importante evaluar la muestra citologicamente. Para ello, habitualmente hacemos un frotis directo y un frotis después de haber centrifugado la muestra a baja velocidad (1.500 rpm).

TÉCNICAS DE COLORACIÓN

Las técnicas de coloración que más usamos en la clínica son la Diff-Quik, y las coloraciones hematológicas de Wright, Giemsa, y May-Grunwald.

INTERPRETACIÓN

Procesos Inflamatorios

Las reacciones inflamatorias se caracterizan por la abundancia de células inflamatorias en la lesión. El tipo de célula que predomina depende del agente etiológico que indujo la inflamación (eg; neutrófilos en infecciones piogénicas, eosinófilos en inflamaciones alérgicas o parasitarias) y del curso del proceso inflamatorio (eg; neutrófilos en la mayoría de los procesos agudos y macrófagos y linfocitos en los procesos crónicos).

Agentes Etiologicos

Ciertos agentes etiológicos son fáciles de identificar en preparados citológicos, incluyendo *bacterias, histoplasma, blastomyces, cryptococcus, coccidioides, aspergillus/penicillium, rickettsias, demodex, y toxoplasma.*

Tumores Malignos

La mayoría de las células somaticas, con excepción de los precursores hemáticos en la médula ósea, son bien diferenciadas. Las células neoplásticas tienen una o más de estas características: aumento de la relación nucleo:citoplasma; cromatina fina; nucléolos; amoldamiento nuclear; uniformidad morfológica; pleomorfismo; vacuolización; anisocitosis; y anisocariosis. Además de esto, las células neoplásticas habitualmente difieren morfologicamente de la población progenitora.

Carcinomas vs. Sarcomas vs. Tumores de Celulas Redondas

Carcinomas

La mayoría de los carcinomas continene células redondas o poligonales que forman grupos (interacción célula a célula). Tienen un citoplasma azul oscuro, y en la mayoría de los adenocarcinomas hay vacuolas evidentes. En los carcinomas espinocelulares, las células aparecen como células individuales.

Sarcomas

Las características típicas de los sarcomas incluyen células fusiformes o poligonales que no se asocian con la célula vecina, que tienen citoplasma rojizo a azulado, y núcleos irregulares. Muchas de las células mesenquimáticas tienen projecciones del citoplasma que semejan velos o colas. Es importante recordar que en un porcentaje variable de sarcomas, las células no exfolian bien, por lo tanto una punción puede dar resultados "negativos". En esos casos, es importante hacer una biopsia quirúrgica.

Tumores de Celulas Redondas

Los tumores compuestos de una población monomórfica de células redondas individuales se denominan tumores de células redondas, e incluyen linfomas, tumores venéreos transmisibles, histiocitomas, mastocitomas, plasmacitomas, y melanomas. Las células en los melanomas y mastocitomas contienen gránulos.

COMO TRATO A MI PACIENTE CON CÁNCER?

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En las ultimas décadas varias modalidades terapéuticas han sido usadas en perros y gatos con cancer, incluyendo cirugía, radioterapia, quimioterapia, immunoterapia, criocirugía, fototerapia, hipertermia, y tratamientos no convencionales, entre otras. Sin embargo, hasta hace dos o tres décadas, la cirugía constituía el principal método de tratamiento en animales con cáncer. Hoy en día, los tumores no-resectables o metastáticos pueden tratarse con variados grados de éxito usando una o más de estas modalidades.

Las primeras cuatro modalidades de tratamiento se describirán en la sección siguiente. Hiperthermia consiste en aplicar calor (comúnmente 42 C) al tumor o al paciente, usando una variedad de métodos; usada por sí misma, es efectiva en gatos con pequeños carcinomas espinocelulares superficiales, y en combinación con radioterapia es beneficioso en algunos perros y gatos con fibrosarcomas y hemangiopericitomas; sin embargo, practicamente no se utiliza. La criocirugía se basa en congelar las células neoplásticas; la liberación de antígenos tumorales estimula una reacción inmunológica local (y probablemente sistémica). La criocirugía se ha usado exitosamente en perros y gatos con pequeños neoplasmas superficiales (e.g.; carcinomas espinocelulares, basaliomas). En la fototerapia, el paciente recibe una droga fotosensibilizante que es eliminada rápidamente en la mayoría de las células normales, pero que se retiene en forma perinuclear en las células neoplasticas. La exposición del tumor a un rayo de laser causa excitación de las moléculas fotosensibilizantes, resultando en liberación de energía y muerte celular. Sin embargo, esta técnica es efectiva sólo en tumores de menos de 0,8 a 1 cm de diámetro o profundidad. La termoquimioterapia consiste en generar temperaturas altas en y alrededor del tumor, al mismo timepo que se administra quimioterapia por vía local o sistémica; la temperatura local alta resulta en captación diferencial del agente antitumoral en las células neoplásticas.

Cuando se evalúa un gato o un perro con un tumor maligno, el clínico se debe dar cuenta que en la mayoría de casos, dada la opción, los propietarios elegirán tratar sus animales. Aunque la eutanasia todavía representa una alternativa razonable para el "tratamiento" de cáncer en animales pequeños, se debe hacer un esfuerzo para investigar otras opciones de tratamiento.

El tratamiento de cáncer puede ser o paliativo o curativo. De ser posible, se deberían erradicar todas las células tumorales en el paciente (obtener una cura) ni bien hecho el diagnóstico. Esto significa acción inmediata, en vez de "esperar-y-ver-que-ocurre". Con muy pocas excepciones, los tumores malignos no regresan espontáneamente. Por lo tanto, demorar el tratamiento en un paciente en el cual se sospecha (o se ha confirmado) un tumor maligno, habitualmente aumenta la probabilidad de que el tumor se disemine localmente o desarrolle metástasis (y por lo tanto disminuye la probabilidad de curar al paciente). La cirugía, la radioterapia, y la hipertermia son tratamientos potencialmente curativos; mientras que la quimioterapia y la inmunoterapia son comúnmente paliativas (ver más adelante).

Como discutimos en el párrafo previo, una vez establecido un diagnóstico de cáncer, la primera decisión que debe hacer el clínico es si el tumor es potencialmente curable. De ser así, se debe hacer un esfuerzo lo antes posible para tratar de eliminar completamente todas las células tumorales. La mayoría de los pacientes con tumores locales (sin metástasis) y algunos pacientes con tumores regionales pueden curarse usando el tratamiento apropiado (cirugía agresiva, radioterapia, o combinaciones de ambos). Ejemplos de estos tumores incluyen, entre otros, fibrosarcomas en perros y gatos, hemangiopericitomas en perros, carcinomas de mama de menos de 2 cm de diametro, y carcinomas espinocelulares de cabeza y cuello en gatos.

Si un paciente tiene un tumor diseminado (linfoma) o un tumor metastático (osteosarcoma, hemangiosarcoma), la probabilidad de lograr una cura es extremadamente baja (< 10%). Sin embargo, en la mayoría de estos pacientes, los tratamientos paliativos resultan en remisiones prolongadas (12 a 18 meses en perros con linfoma ú osteosarcoma tratados con quimioterapia, o cirugía/ quimioterapia, respectivamente). Ciertos tumores, como los tumores venéreos trasmisibles, habitualmente se curan con quimioterapia (vincristina).

Si el clínico juzga que el paciente no puede ser curado, debe tomar la decisión de usar tratamiento paliativo o no. En este momento, es apropiado discutir la eutanasia (como una alternativa potencial) con el propietario.

Dependiendo del tipo de tumor, su comportamiento biológico, y su "staging", se pueden recomendar una o más de las opciones que hemos discutido. Sin embargo, se debe recordar que además de los factores relacionados al tumor (tipo histopatólogico y grado de diferenciación, "staging" o grado de diseminación, la respuesta a tratamientos específicos), hay una multitud de factores que influyen la selección del tratamiento óptimo.

Es importante recordar que el mejor tratamiento para un tipo particular de tumor no constituye necesariamente el mejor tratamiento para un propietario o paciente en particular. El factor más importante a considerar en el paciente es su actividad y salud general (o escala de perfomance)(Tabla). Por ejemplo, un gato o perro con actividad notablemente disminuida y signos constitucionales severos (pobre escala de perfomance) no constituye un candidato bueno para usar quimioterapia agresiva o para las anestesias repetidas que se necesitan para utilizar radioterapia.

En el paciente con un tumor, las dos metas principales de tratamiento paliativo de cáncer son la inducción de remisión y la buena calidad de vida. La remisión se refiere a una disminución en la masa tumoral. Si no se puede mantener una buena calidad de vida, el tratamiento se debe modificar o interrumpir.

Finalmente, la mayoría de los gatos y perros con cáncer se tratan usando un enfoque de equipo. Este equipo incluye el paciente, el propietario, el oncólogo clínico, el cirujano oncológico, el radioterapista, el patólogo clínico, y el patólogo. La interacción entre los miembros del equipo resulta en beneficios marcados para el animal afectado y sus propietarios.

Tabla 1. Escala de perfomance de Karnofsky para perros y gatos.

Grado de Actividad	
0 - Normal	Totalmente activo, actividad similar an antes de enfermarse
1 - Restringido	Actividad restringida en comparación con antes de enfermarse, pero capaz de funcionar como un animal aceptable
2 - Actividad comprometida	Severamente restringida; ambulante únicamente para comer, defecando y orinando en áreas aceptables
3 – Incapacitado	Completamente incapacitado; debe ser alimentado a fuerza; incapaz de restringir orina y defecación a áreas aceptables
4 - Muerto	

MEDICINA INTERNA: DISCUSSION DE CASOS CLÍNICOS

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Utilizaremos la siguiente información durante la discusión de casos clínicos

.BIOQUIMICA

Análysis	Alto	Bajo
Urea	Azotemia renal, prerenal, o postrenal Dieta Hemorragia GI	Insuf. hepática Shunt PS Dieta Diuresis
Creatinina	Azotemia renal, prerenal, o postrenal Raza (galgos) Dieta	NS
Fósforo	Azotemia renal, prerenal, o postrenal Intoxicación Sindr. de lisis tumoral	Insulina Alimentación enteral o parenteral
Calcio	Tumores IRC Intoxicación Addison Hipervitaminosis D Hiperparatiroidismo	Eclampsia Hipoparatirodismo
Sodio	Deshidratación Diabetes mellitus Fluidoterapia	Addison Intoxicación por agua SNC Diuresis postobstrucción
Potasio	Addison IRA/IRC Drogas (furosemida, propanolol)	Diuresis postobstrucción Dieta Anorexia? Fluidoterapia Vómitos/diarrea Cetoacidosis
Cloro	Deshidratación Diabetes mellitus Fluidoterapia	Vómitos Intoxicación por agua Diuresis postobstrucción
Bicarbonato	Alcalosis metabólica Acidosis respiratoria	Acidosis metabólica Alcalosis respiratoria
ALT (GPT)	Lesion hepatocelular Miopatía	NS
AST (GOT)	Lesion hepatocelular Miopatía	NS
FA	Hiperadrenocorticismo Colestasis Drogas (corticoides, barbitúricos) Tumores (linfoma)	NS
FA-Esteroides	Hiperadrenocorticismo Drogas (corticoides, barbitúricos) Tumores (linfoma)	NS
CK	Miopatía Anorexia prolongada (gatos) Tromboembolismo aórtico (gatos) Rabdomiolisis (galgos)	NS

Colesterol	Hipotiroidismo Hiperadrenocorticismo Sindr. hiperlipidemia (Schnauzers) Sindr. nefrótico	NS
Bilirrubina	Hemólisis Hepatopatía Colestasis Hemorragia interna	NS
Proteína	Deshidratación Gamopatías	Enteropatía Nefropatía Hepatopatía Hemorragia
Albúmina	Deshidratación	Enteropatía Nefropatía Hepatopatía Hemorragia
Globulina	Gamopatía policlonal (inflamación, infección) Gamopatía monoclonal (mieloma, LLC, PIF, ehrlichia, leishmania)	Enteropatía Hemorragia Inmunodeficiencia (B)

QUIMIOTERAPIA DE REINDUCCION EN EL PERRO CON LINFOMA

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Linfoma (linfosarcoma, LSA) es el tumor hemolinfático más común en el perro. La forma anatómica de presentación más común es la multicéntrica, en la cual linfadenopatía generalizada masiva (ocasionalmente asociada con hepato-esplenomegalia) es el signo cardinal. En algunos pacientes las lesiones extranodales son comunes (piel, sistema nervioso central, riñón). El diagnóstico de linfoma multicentrico es relativamente sencillo, ya que la aspiración por aguja fina revela una población monomórfica de células linfoides neoplásticas. El fenotipo del tumor tiene implicaciones pronósticas; en el perro, los pacientes con linfoma de células B tienen major pronóistico que los de células T.

Como los linfomas son tumores sistémicos, el mejor tratamiento es la quimioterapia, ya que es efectiva, práctica, y tiene muy poca toxicidad. Con los protocolos de quimioterapia de combinación, la mayoría de los perros con linfoma sobreviven más de un año, y aproximadamente el 25-30% sobreviven más de 2 años (con excelente calidad de vida). La sobrevida promedio de los perros con linfoma que no reciben tratamiento es de aproximadamente 30 días.

El tratamiento de perros con linfoma habitualmente consiste de 4 fases diferentes: **inducción de remisión, mantenimiento, intensificación**, y **re-inducción de remisión**. Durante la **inducción de remisión**, el paciente recibe una combinación de 3 ó 4 drogas, de las cuales una ó más son inyectables; la duración de esta fase varía entre 8 y 12 semanas. Si al final de esta fase, el paciente no está todavía en remisión completa, utilizamos una breve fase de **intensificación**, en la cual administramos una ó dos drogas adicionales con la intención de consolidar la remisión. Una vez que el paciente está en remisión, utilizamos la fase de **mantenimiento**, en la cual administramos dosis bajas de quimioterapia (habitualmente por vía oral), durante un período prolongado. Cuando el tumor sale de remisión, el paciente es tratado con un protocolo de **re-induccion de remisión.**

Otro enfoque terapéutico es utilizar un protocol de quimioterapia más agresivo, sin terapia de mantenimiento. Habitualmente se usan protocolos tipo CHOP (con doxorubicina), durante 3 a 5 meses; el protocolo de la Universidad de Wisconsin es uno de los que se usa más comunmente.

Los protocolos que utilizamos en el Ohio State University Veterinary Teaching Hospital estan en la tabla siguiente.

1) **Inducción de remisión:**
- **Protocolo COAP**:
  - ciclofosfamida (Endoxan) 50 mg/m^2, PO, día por medio en perros, o 200-300 mg/m^2 cada 3 semanas en gatos
  - vincristina (Oncovin) 0.5 mg/m^2 SA, IV, q/1 semana
  - arabinosido de cytosina (Cytosar-U) 100 mg/m^2/day, goteo IV or SQ, durante los 2 primeros días en gatos y los 4 primeros días en perros
  - prednisona 50 mg/m^2, PO, SID durante la primera semana; después 20 mg/m^2 PO, día por medio

ESTE PROTOCOLO SE UTILIZA DURANTE LAS PRIMERAS 8 SEMANAS. DESPUES SE UTILIZA UNO DE LOS PROTOCOLOS DE MANTENIMIENTO.

2) **Intensificación**:
- l-asparaginasa (Elspar) 10,000-20,000 IU/m^2, SQ (una sóla dosis)

3) **Mantenimiento**:
- **Protocolo LMP**:
  - clorambucilo (Leukeran) 20 mg/m^2, PO, cada 2 semanas
  - metotrexato 2.5 mg/m^2, PO, 2 ó 3 veces por semana*
  - prednisona 20 mg/m^2, PO, día por medio
- **Protocolo COAP**:
  - usar como descripto más arriba, pero cada 2 semanas durante 4 ciclos, después cada 3 semanas, y así sucesivamente.

4) **Re-inducción de remisión**:
- **Protocolo D-MAC:** (repetir continuamente durante 12-16 semanas)
  - dexametasona 1 mg/kg, PO ó SQ en los días 1 y 8
  - actinomicina D 0.75 mg/m^2, IV en el día 1
  - arabinosido de cytosina 200-300 mg/m^2, goteo IV durante 4 horas, en el día 1
  - melfalan (Alkeran) 20 mg/m^2, PO, en el día 8 ***(después de 3-4 dosis, usar clorambucilo a la misma dosis en vez de melfalan)***

*The author currently uses the higher dose every other week, since it is not associated with significant toxicity and appears to maintain longer remissions.

Tabla 1. Protocolo de la Universidad de Wisconsin UW 19 (sin mantenimiento)

semana 1:	incristina 0.5–0.75 mg/m^2, IV asparaginasa 400 IU/kg IM o SQ prednisona 2 mg/kg PO q24h
semana 2:	iclofosfamida 200–250 mg/m^2, IV o PO prednisona 1.5 mg/kg PO q24h
semana 3:	incristina 0.5–0.75 mg/m^2, IV prednisona 1 mg/kg PO q24h
semana 4:	doxorubicina 30 mg/m^2 (o 1 mg/kg si <10 kg) IV prednisona 0.5 mg/kg PO q24h
semana 5:	NADA
semana 6:	vincristina 0.5–0.75 mg/m^2, IV
semana 7:	ciclofosfamida 200–250 mg/m^2, IV o PO
semana 8:	vincristine0.5–0.75 mg/m^2, IV
semana 9:	doxorubicina 30 mg/m^2 (o 1 mg/kg si <10 kg) IV
semana 10:	NADA
semana 11:	vincristina 0.5–0.75 mg/m^2, IV
semana 12:	ciclofosfamida 200–250 mg/m^2, IV o PO
semana 13:	vincristine 0.5–0.75 mg/m^2, IV
semana 14:	doxorubicina 30 mg/m^2 (o 1 mg/kg si <10 kg) IV
semana 15:	NADA
semana 16:	vincristina 0.5–0.75 mg/m^2, IV
semana 17:	ciclofosfamida 200–250 mg/m^2, IV o PO
semana 18:	vincristina 0.5–0.75 mg/m^2, IV
semana 19:	doxorubicina 30 mg/m^2 (o 1 mg/kg si <10 kg) IV

DIABETIC KETOACIDOSIS IN DOGS

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'Tis not amiss, ere ye're giv'n o'er, To try one desp'rate med'cine more, For where your case can be no worse, The desp'rat'st is the wisest course.
—Samuel Butler, Epistle of Hudibras to Sidrophel, 1664

Diabetes mellitus is a relatively common disease in dogs. When well regulated, owners have little problem managing the condition. However, in a patient that has not previously been diagnosed, or in a dog that has developed complications such as pancreatitis, diabetic ketoacidosis can result. This metabolic nightmare creates a multitude of fluid, electrolyte, and acid–base irregularities that can quickly turn fatal if not properly managed. In this article, these issues are addressed, problem by problem, followed by a discussion of how they might be corrected.

CLINICAL PRESENTATON OF DIABETIC KETOACIDOSIS (DKA)

The dog with DKA is usually very, very sick. Most dogs present with a history of vomiting, lethargy, and anorexia for a variable period of time (1–5 days). On physical exam, the dog is often clinically dehydrated and depressed. Ketones, smelling like acetone (nail polish remover), can often be detected on the dog's breath. For many people with a "nose" for smelling ketotic breath odor, this is almost pathognomonic for DKA. Other findings could include abdominal pain or icterus (if the dog has concurrent pancreatitis).

The initial workup for a patient suspected of having DKA includes a complete blood count, serum chemistry panel (including lipase), and urinalysis. A urine culture is also helpful. Blood gas analysis can assist in determining optimal fluid therapy choices.

The care of a patient with DKA requires intensive, 24-hour monitoring and in-house laboratory availability for electrolytes, glucose, and blood gases. In many cases, a referral center or emergency/critical care clinic is the optimal choice for a patient with DKA.

The individual metabolic disturbances seen in DKA are addressed in the following sections. We will cover how to correct the imbalance individually, and then summarize the care and monitoring of dogs with DKA.

FLUID DEFICITS

Dehydration is a common problem in patients with DKA. Hyperglycemia causes an osmotic diuresis, and most dogs are unable to keep up with losses by drinking. Additionally, vomiting is very common, worsening fluid losses.

Aggressive fluid therapy should be instituted quickly. Crystalloid fluids are used to treat dogs with DKA. Either 0.9% NaCl or lactated Ringer's solution can be used, and the choice can be based on the initial electrolyte values. If severe hyponatremia is noted, then sodium chloride is a preferred fluid choice. It is often given at a rate designed to recover any dehydration deficit over 10 to 24 hours, in addition to meeting maintenance fluid needs.

METABOLIC ACIDOSIS

In the absence of insulin, glucose transport into cells cannot occur, and the body is in a state of starvation. To cope with this condition, fatty acids are mobilized from adipocytes and transported to the liver. In the liver, the fatty acids are oxidized in the mitochondria into ketone bodies, which can be used by most cells as an alternative energy source. However, the ketone bodies are acidic, and therefore contribute to a high anion gap acidosis. Vomiting, common in most patients with DKA, can also contribute to the metabolic acidosis.

The metabolic acidosis can be quite severe, and patients with blood pH values around 7.0 are not uncommon. Blood gases are the ideal way to identify a metabolic acidosis, but evaluating the bicarbonate concentration on a chemistry panel can also help.

There are several ways to treat metabolic acidosis in the patient with DKA. Some clinicians use sodium bicarbonate routinely, but I prefer to correct the underlying reason for the acidosis by treating with insulin. By providing insulin, glucose is able to enter cells, and production of ketones stops. This quickly leads to resolution of the acidosis. Additionally, treating the patient with an alkalinizing fluid such as lactated Ringer's solution in volumes sufficient to treat dehydration will help resolve metabolic acidosis.

INSULIN DEFICIENCY

Providing insulin is important for many reasons. It stops production of ketone bodies, thus resolving acidosis. It provides the means for energy delivery to the brain, which requires glucose as its only energy source. It also allows for the reduction of severe hyperglycemia, which can result in a severe hyperosmolar condition.

In the ketoacidotic patient, the insulin preparation required is regular insulin, since it has a short duration of action and therefore can be tightly controlled in the sick patient. It can be given intermittently or as an IV infusion. My preference is to give insulin as an IV insulin infusion (Table 1). When giving an insulin infusion, it is important to discard the first 50 mL, since insulin adheres to plastic. The infusion is given and the blood glucose is periodically monitored. When the blood glucose drops to a safer level, then glucose is added to the intravenous fluids and the insulin infusion rate is slowed as needed.

POTASSIUM IMBALANCE

In the patient with DKA, laboratory values for potassium may be high, low, or normal. However, it can safely be assumed that almost all patients with DKA suffer from a whole-body depletion in potassium. Because of the acidosis, intracellular potassium is "traded" for extracellular hydrogen, raising the extracellular potassium, which often is excreted. When insulin is given (correcting the acidosis),

Table 1. Intravenous Insulin Infusion

1. Add 2.2 units/kg body weight of insulin to 250 mL 0.9% sodium chloride intravenous fluids.
2. Connect all needed IV fluid lines which will be used to deliver the infusion to the patient.
3. Open the infusion and discard 50 mL of the infusion, allowing insulin to saturate the tubing.
4. Connect to the patient, and infuse the insulin solution at 10 mL/hour via an infusion pump.
5. Monitor blood glucose initially every 1–2 hours.
6. When blood glucose falls below 250 mg/dL (13.88 mmol/L), decrease insulin infusion rate by 25–50% and provide IV fluids containing 2.5–5% glucose.
7. If blood glucose falls below 100, then the insulin infusion is temporarily stopped.

hydrogen and potassium ions switch back, and potassium is driven intracellularly. This inevitably results in a drop in potassium concentration.

Therefore, potassium supplementation of fluids should be performed even if there is not laboratory evidence of hypokalemia at initial presentation. The amount of potassium supplementation is commensurate with the initial potassium value, but should never exceed 0.5 mEq/kg/hr.

PHOSPHORUS AND MAGNESIUM IMBALANCE

Once insulin therapy has commenced, decreased concentrations in phosphorus and magnesium may become problematic. When insulin is available and glucose enters cells, phosphorus goes intracellularly as well, and this may create an extracellular deficit of phosphorus. Clinical effects of hypophosphatemia include hemolytic anemia and neuromuscular signs such as weakness. If serum phosphorus concentrations drop below 2.0 mg/dL (0.65 mmol/L), then phosphorus supplementation should be instituted using potassium phosphate. The amount of potassium provided by this preparation needs to be subtracted from any needed potassium supplementation being provided.

Magnesium deficiency may be difficult to diagnose in dogs with DKA. It may occur secondary to decreased oral intake and increased renal loss. Severe magnesium deficiency may result in neuromuscular weakness and cardiac arrhythmias. If needed, magnesium can be supplemented in an IV solution of magnesium chloride.

DKA: ADMISSION TO DISCHARGE

Let's imagine an 8-year-old, female spayed mixed breed dog named "Example" with a 6-week history of polyuria/polydipsia and weight loss. In the past week she has been progressively more lethargic and inappetent, with 48 hours of severe illness and vomiting.

On exam, Example weighs 10 kg, has a temperature of 98.5°F, pulse rate of 140 bpm, and respiratory rate of 24 per minute. She is very depressed and about 10% dehydrated. She has an obvious ketone odor to her breath. Heart and lungs sound normal, and abdominal palpation is normal. No other abnormalities are detected on physical exam.

We obtain blood for an in-house CBC, chemistry panel, electrolytes, and blood gases. We obtain urine for a urinalysis and urine culture. While we await those results (about 20 minutes), our technicians place a double-lumen jugular catheter. This catheter allows us to administer glucose-containing fluids in one line, and administer other fluids (such as an insulin infusion) and periodically sample blood through the other line.

The CBC shows a mild mature neutrophilia. The chemistry panel shows elevations in liver enzymes, and a blood glucose of 522 mg/dL (28.98 mmol/L). Sodium and potassium values were both in the normal range. Bicarbonate was low at 12 IU/L (12 U/L). Blood gases confirmed a metabolic acidosis.

We calculated Example's fluid deficit at 1000 mL, which we chose to correct over 12 hours at 83 mL/hr. Her fluid losses from vomiting were estimated at 10 mL/hr. Her maintenance fluid needs were 27 mL/hr. Therefore, her initial fluid rate was 120 mL/hr. We chose to use lactated Ringer's solution, and supplement it with 30 mEq KCl/L, since the initial potassium concentration was normal, but we assumed her total body potassium was low. At a rate of 120 mL/hr, the potassium was being infused at (0.3 x 120) = 3.6 mEq/hour, which is safely below the limit of 0.5 mEq/kg body weight per hour (in Example's case, this would be 5.0 mEq/hour).

We then set up her insulin infusion. We added 2.2 units/kg of regular insulin (in Example's case, 22 units) to a 250 mL bag of 0.9% saline, hooked up an infusion set, and discarded the first 50 mL. We initiated the insulin infusion in the other jugular line at 10 mL/hr, decreasing the other line's fluid rate by 10 mL/hr.

After two hours, we rechecked her blood glucose. It had dropped to 343 mg/dL (19.04 mmol/L), and her body temperature was 100.1°F. After 4 hours, her blood glucose was 219 mg/dL (12.07 mmol/L), sodium and chloride were normal, and potassium had dropped to 2.9 mEq/L (2.9 mmol/L). Her fluid was switched to 0.45% NaCl with 2.5% dextrose supplemented with 40 mEq KCl/L, and her insulin infusion was decreased to 7.5 mL/hour. Over the next 12 hours, her blood glucose was checked every 2 hours, and her insulin infusion was changed up or down by 25% to keep her blood glucose between 150 and 300. After 12 hours, her fluid rate was changed back to maintenance fluids, since her dehydration seemed to be resolved.

Twenty-four hours after admission, Example seemed brighter and more alert. She last vomited 12 hours before. She no longer had ketotic breath odor and was normothermic with a normal heart rate. Her electrolytes were normal, and her blood glucose was 241 mg/dL (13.38 mmol/L). She was offered small amounts of water every hour, which she drank eagerly without vomiting. Later that day, she was offered a small amount of a bland canned dog food, which she ate. She continued on the fluids and insulin infusion overnight, with glucose checks reduced to every 4 hours.

Forty-eight hours after admission, Example was very bright and alert. She was offered food and ate eagerly, so she was given 6 units of NPH insulin subcutaneously, and the IV insulin infusion was stopped. Water was offered at all times. Blood glucose 6 hours after insulin was 151 mg/dL (8.38 mmol/L), and 12 hours after insulin it was 278 mg/dL (15.43 mmol/L). An evening dose of 7 units NPH insulin was given subcutaneously, and she was fed.

Seventy-two hours after admission, Example was very clear that she wanted to go home. Her morning glucose was 244 mg/dL (13.54 mmol/L), and she was eating and drinking well. Her jugular catheter was removed, and she was given 7 units of NPH insulin subcutaneously. She was discharged to her owners with instructions on insulin administration, and the plan was for the owners to administer 7 units of NPH insulin twice a day, with changes as needed.

Example did very well. She recovered quickly, and had few complications. She did not have any problems with phosphorus or magnesium, and did not have other diseases that make treatment more difficult, such as pancreatitis or a severe infection such as pneumonia or pyelonephritis. But, that's why she's an Example! In real life, things seldom go quite that easily. What is true about treating the patient with DKA is that anticipation of complications is the best treatment. If you anticipate problems such as hypokalemia and acidosis, then early treatment will often result in lifesaving results.

CANINE HYPOTHYROIDISM: MYTH VERSUS REALITY

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Authors almost always refer to hypothyroidism as a common (if not the most common) endocrine disease in dogs, and, while it may be true, there is little evidence to support this claim. In fact, canine hypothyroidism may be one of the most over-diagnosed diseases in small animal medicine. Just about any medical disorder can be associated with decreases in circulating concentrations of thyroid hormone, causing hypothyroidism to be over-diagnosed. In addition, it is common practice for veterinarians to treat hypothyroidism empirically following a presumptive diagnosis. This practice is not recommended for several reasons. First of all, it is not scientifically sound medical practice. Second, it may allow another disorder to progress undiagnosed. Third, unnecessary supplementation with thyroid hormone disrupts the normal regulation of thyrotropin-releasing hormone (TRH), thyroid-stimulating hormone (TSH), and thyroid hormone production, the consequences of which are not understood.

Clinical signs of hypothyroidism result from generalized decreases in metabolic functions supported by thyroid hormone action. The clinical signs of hypothyroidism are multisystemic and varied. Their onset is gradual. The classic presentation of a hypothyroid dog includes obesity, inactivity, mental dullness, decreased appetite, dermatologic abnormalities, and intolerance to exercise and cold. These signs may or may not be present in all dogs with hypothyroidism.

Dermatologic abnormalities are the most common presenting complaints of owners of dogs with hypothyroidism. Approximately 85% of hypothyroid dogs are reported to have skin lesions. Care should be taken in interpreting the reports of the prevalence of dermatologic signs in canine hypothyroidism because many of the reports have been written by dermatologists. Whatever the true incidence of these signs, they include alopecia (arrest of hair growth cycle in the telogen phase), dryness, scaling, dull hair which is easily epilated, seborrhea, slow hair re-growth, various degrees of hyperpigmentation, poor wound healing. In extreme cases, mucopolysaccharides accumulate in the skin causing it to thicken, especially in the face. This condition is called *myxedema*. Dogs with myxedema are classically referred to as having “tragic” facial expressions. The typical skin problem of canine hypothyroidism is usually not pruritic, although secondary bacterial infections are possibly, and could cause a degree of pruritis. Hypothyroidism is also commonly mentioned as an underlying cause of chronic ear infection. There is little or no scientific support for this claim.

MYTH OR REALITY: HYPOTHYROIDISM IS A CAUSE OF OTITIS

Hypothyroidism is commonly cited as a cause of bacterial pyoderma, which can occur locally, manifesting as otitis externa (infection of the outer ear). In a recent paper the author stated, “Recurrent bacterial and yeast infections of the skin and ears often occur secondary to hypothyroidism and may be the only presenting signs,” although the statement is not supported by any reference to a published study. It is commonly stated in articles and textbooks that hypothyroidism can cause decreased function of lymphoid cells, decreased T-cell function, decreased humoral immunity, and decreased barrier function of the skin. Evaluation of these statements and associated references shows a considerable lack of supportive evidence. Authors' personal observations are commonly cited, as is one research paper in mice published in 1980. Examination of that reference reveals that it is not a study of hypothyroidism at all, but rather a study of the effects of thyroid hormone excess on the immunologic response to administration of sheep red blood cells in mice. The effects were minimal. While there are some studies (not in dogs) showing that thyroid hormone has some effects on the immune system, athyreotic human patients have been shown to have similar white blood cell function when compared with normal controls. There is no published evidence to suggest that otitis externa, especially as the sole clinical sign, is a feature of hypothyroidism in dogs.

MYTH OR REALITY: HYPOTHYROIDISM IS A CAUSE OF NEUROLOGIC DISEASE

Many neurological signs have been blamed on hypothyroidism in dogs. Bicshel et al reported 4 dogs with neurological diseases associated with low concentrations of serum total T4 and inadequate responses to exogenous TSH administration. Three of the dogs had no non-neurological clinical signs of hypothyroidism. One was a 7-year-old boxer with facial paralysis that was also treated with sulfamethoxazole, a drug known to cause severe hypothyroidism. Another was an 11-year-old Old English sheepdog with a head tilt that did not resolve on thyroxine therapy. Another was a 10-year-old cocker spaniel with circling and a head tilt that did not respond to thyroxine therapy, and the other was a 10-year-old mixed breed dog with vestibular signs (head tilt, abnormal eye movements, loss of balance) that resolved. Idiopathic vestibular disease, which is clinically similar, is common in older dogs, and resolves spontaneously as well. In another paper by Jaggy et al, 29 dogs with hypothyroidism (diagnosed by TSH stimulation testing) and neurologic signs were studied retrospectively. Eight of nine dogs with vestibular disease recovered on thyroxine replacement therapy. Four dogs with megaesophagus did not recover despite thyroxine therapy. Of the 29 dogs studied, only 10 had increased concentrations of serum cholesterol. This common biochemical finding is usually present in more than 75% of dogs with hypothyroidism, leaving room for doubt that many of the dogs in the study actually had hypothyroidism.

But what about the TSH stimulation test results in the dogs with reported hypothyroidism and neurological disease? The TSH stimulation test is not perfect, and even though it is considered a gold standard test for hypothyroidism, it can be difficult to interpret. Even its position as a gold standard is in question. A recent study of dogs with low T4 and thyroid biopsy results showed that the TSH stimulation test is often false positive. This report also supported earlier reports showing the overlap between total T4, free T4, and endogenous TSH concentrations in sick versus hypothyroid dogs.

MYTH OR REALITY: HYPOTHYROIDISM IS A CAUSE OF INFERTILITY

Hypothyroidism has been implicated as a cause of infertility in both male and female dogs. It should be noted that the most common reason for infertility in dogs is mistiming of breeding. Still, bitches failing to conceive are often treated empirically with thyroid hormone supplementation. Early investigators reported sperm abnormalities in dogs with hypothyroidism. More recent studies have shown no effect of experimentally induced hypothyroidism on testicular size, sperm count, motility, or morphology, although actual fertility studies have not been done.

MYTH OR REALITY: HYPOTHYROIDISM IS A CAUSE OF AGRESSION

Recently, hypothyroidism has been implicated as a cause of aggression in dogs. Only a handful of cases appear in the literature. In all cases, physical examination findings and results of CBC and biochemistry profiles were normal. All dogs had low serum T4 and high TSH concentrations. All but one were intact males. One dog responded to thyroid supplementation, but was also castrated and subjected to behavioral modification therapy. The other dogs did not respond to treatment.

MYTH OR REALITY: VACCINES CAUSE HYPOTHYROIDISM

Hypothyroidism is an immune-mediated disease, and attempts have been made to blame the presence of canine immune-mediated diseases on over-vaccination. In one study, dogs were vaccinated repeatedly at 8, 10, 12, 16, 20, 26, and 52 weeks of age and antibodies against thyroglobulin were studied. Thyroglobulin is a key protein involved in thyroid hormone production, and antibodies against this protein are routinely measured as a test for the presence of an immune-mediated thyroiditis. In the study, antibodies were higher in excessively vaccinated dogs than in control dogs. In a subsequent study by the same authors, however, the thyroid glands of over-vaccinated dogs were not different from unvaccinated dogs. If anti-thyroglobulin antibodies truly do indicate the presence of lymphocytic thyroiditis (the most commonly cited type of immune-mediated thyroid disease causing hypothyroidism), there should have been more inflammation found in the over-vaccinated dogs. There are lots of possibilities for why antibody tests could be positive when there is no underlying immune-mediated thyroid disease, but it cannot be explained in the context of hypothyroidism.

HOW IS HYPOTHYROIDISM DIAGNOSED?

The measurement of both total T3 and total T4 are commonly performed in canine practice. There is diagnostic value to the determination of TT4, because a finding of a normal TT4 excludes a diagnosis of hypothyroidism. The finding of a low basal TT4, however, is of little diagnostic value, because TT4 concentrations are falsely lowered by just about any concurrent illness, and by a large number of drugs, including benzodiazepines, phenobarbital, glucocorticoids, imidazoles, penicillins, sulfonylureas, salicylates, and phenothiazines. Unfortunately, many dogs are diagnosed with hypothyroidism based only on findings of low TT4 concentrations. Measurement of serum TT3 is without value in the diagnosis of thyroid disorders in dogs.

Most thyroid hormone circulates bound to plasma protein. Approximately 1% of TT4 is not protein-bound and is referred to as free T4. In true hypothyroidism, basal free T4 concentrations should be low, and most of these measurements in hypothyroid dogs are low. There is, however, a degree of overlap with normal dogs and dogs with non-thyroidal illness, so this test alone does not confirm a diagnosis of hypothyroidism.

The combination of free T4 and serum TSH measurement is considered nearly 100 percent diagnostic for hypothyroidism in people. Unfortunately, the results of serum TSH measurement are not nearly as clear-cut in canine hypothyroidism. Most dogs with primary hypothyroidism, as expected, have high concentrations of TSH in the serum. Serum TSH concentrations, however, are normal in some dogs with hypothyroidism, making this test less reliably in this species.

Thyroid autoantibodies—antibodies against thyroglubulin, T4 and T3—are considered to be a marker for lymphocytic thyroiditis. Probably the most consistent, although by no means absolute, antibody found in dogs with hypothyroidism is anti-thyroglobulin antibody. This test may be of some use, when combined with other findings, in the diagnosis of hypothyroidism. False positives and false negatives occur.

In the past, the most reliable test for canine hypothyroidism was the TSH stimulation test. Exogenous TSH administered to a normal dog causes a consistent rise in the serum concentration of TT4, whereas dogs with hypothyroidism exhibit little or no response to TSH. While there were plenty of gray areas in interpreting this test, it was considered a very useful diagnostic tool. Recent work has called the validity of the test into question and has suggested that quantitative scintigraphy may be the most accurate test.

Therapeutic trials are often recommended for diagnosis of hypothyroidism in dogs, but caution is warranted in the interpretation of test results. Regrowth of hair, for example, following thyroid hormone supplementation does not necessarily implicate thyroid hormone deficiency as a cause of alopecia. Studies have shown that thyroid hormone accelerates hair growth and wound healing in euthyroid mice and rats. It's possible, if not probable, that thyroid hormone stimulates these processes in euthyroid dogs as well.

Short of being confirmed by an invasive diagnostic procedure such as a thyroid biopsy, a diagnosis of hypothyroidism in a dog should depend on the finding of appropriate clinical signs, a low free T4, and some of the following results: high TSH, positive anti-thyroglobulin antibodies, hypercholesterolemia. Less stringent criteria may result in the overdiagnosis of the disease.

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METHIMAZOLE TRIALS EXPOSED

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Hyperthyroidism is one of the most commonly diagnosed disorders of domestic cats. As our knowledge and experience in diagnosing and treating the disease has grown, certain challenges have become apparent. Diagnosis is often straightforward, but cases of occult hyperthyroidism are increasingly recognized and can present a diagnostic challenge. Treatment options for feline hyperthyroidism have not changed substantially in recent years, but awareness of adverse effects of treatment has grown, especially regarding the effects of treatment on renal function.

Investigators have shown consistently that treatment of hyperthyroidism can have deliterious effects on renal function in cats, and that feline hyperthyroidism can mask underlying chronic renal insufficiency. Post-treatment renal failure is common, occurring in 17% to 38% of cats treated for hyperthyroidism. Treatment of hyperthyroidism by bilateral surgical thyroidectomy causes a consistent, and sometimes disastrous, drop in glomerular filtration rate (GFR).[1] The same is true for radioiodine treatment and methimazole. This clinical problem has led to the use of "methimazole trials" prior to radioiodine or surgical thyroidectomy. Especially in cats with impaired renal function, methimazole is often considered the most logical first-line treatment for hyperthyroidism because it can be reversed if renal failure ensues.

WHICH CATS SHOULD UNDERGO METHIMAZOLE TRIALS?

There are many different recommendations for how and when methimazole trials should be performed. Unfortunately, there are few published data to guide these decisions. For example, veterinarians, general practitioners and specialists alike, commonly recommend methimazole trials only for cats with questionable renal function. There is a commonly held belief that cats with well-concentrated urine (urine specific gravity > 1.035) have adequate renal function and do not run a significant risk of post-treatment renal insufficiency and that methimazole trials are not needed in these cats. There are no published data to support this opinion, and its wisdom should be questioned. First, urine specific gravity is an unreliable predictor of renal function in cats because thyroid hormone can cause polydipsia and polyuria as a primary effect, regardless of renal function. Second, urine specific gravity is not a measure of GFR, but rather an indicator of renal tubular function. It is unknown if hyperthyroid cats with concentrated urine are at a lower risk of post-treatment renal failure. We looked at 24 hyperthyroid cats developing overt renal insufficiency within 2 to 3 months of radioiodine treatment in our hospital; 13 (54%) had urine specific gravity measurements greater than 1.035. Five of those cats (21%) had urine specific gravity measurements above 1.050 (unpublished data). We suspect, therefore, that urine specific gravity should not be used as a predictor of post-treatment renal status in hyperthyroid cats, and that a methimazole trial should be recommended for any hyperthyroid cat that can tolerate the drug.

HOW LONG SHOULD A TRIAL RUN?

There are no published studies that have determined the best length of time for a methimazole trial. Studies in which GFR has been measured in cats treated for hyperthyroidism have typically examined renal function before and 30 days after treatment. It is not known whether there is a further decline in GFR after this initial treatment period, or whether the decline in GFR is permanent. My opinion is that a 30-day period is adequate, but that is based on clinical experience rather than on scientific results. It should also be noted that a good response to a trial with methimazole does not guarantee that a given cat will not experience overt renal insufficiency with subsequent radioiodine treatment. In our hospital we have seen several cats with hyperthyroidism well controlled on methimazole and with well-concentrated urine and normal serum creatinine and urea nitrogen concentrations that developed overt renal insufficiency shortly after radioiodine therapy. Some have speculated that a more gradual drop in circulating thyroid hormone concentrations with anti-thyroid drugs versus radioiodine may explain this situation. Also, methimazole may have some renal protective effects in cats as has been shown in other species.[8,9]

ARE THERE OTHER PREDICTORS OF RENAL FAILURE?

Despite the recommendation of some experts, there is no strong evidence to support the notion that cats with urine specific gravity measurements about 1.035 are not at risk for renal insufficiency following treatment of hyperthyroidism, but it is unknown whether there are other predictors. Our group has examined many cases of post-treatment renal failure looking for pretreatment predictors, and we have not been able to find anything useful. Investigators have reported that pretreatment GFR measurement may be useful as a predictor of post-treatment renal status in hyperthyroid cats. In one report cats that underwent treatment for hyperthyroidism and did not develop renal insufficiency all had pretreatment GFR measurements of greater than 2.25 mL/kg/min. The authors concluded that pretreatment GFR was a valuable predictor of post-treatment renal insufficiency. We looked back at our original published reports of GFR in cats with hyperthyroidism, and found that 3 of 5 hyperthyroid cats experiencing post-treatment renal insufficiency had pretreatment GFRs greater than 2.5 mL/kg/min.[1] We found no significant difference between GFR in cats that did or did not experience post-treatment renal insufficiency. Because of these two conflicting reports, it is probably unwise to consider a given cat safe from harm if the pretreatment GFR is >2.25 mL/kg/min. Differences in methods of determining GFR may account for these disparate reports, but we do not believe there is adequate published evidence to rely on GFR measurement to predict post-treatment renal insufficiency in hyperthyroid cats. Furthermore, measurement of GFR in cats is difficult. Most accepted methods of GFR estimation are not available to the majority of small animal practitioners, so a methimazole trial would be considerably more practical.

HOW A METHIMAZOLE TRIAL IS DONE

While the time necessary to see if treatment of hyperthyroidism will cause overt renal insufficiency has yet to be determined, there is adequate evidence to suggest that 30 days is a reasonable time. A common mistake, however, is failure to recheck serum thyroid hormone concentrations during the trial. Because the half-life of T4 in the cat is less than 8 hours, I typically recheck cats one week after starting a trial. If the T4 is not in the lower half of the normal range (optimal for hyperthyroidism control), the dose is increased and the on-month period is started again. Often the dose of methimazole needs to be adjusted to achieve euthyroidism, and the goal is to have euthyroidism for a month, not just methimazole for a month. Because of the danger of developing other side effects to methimazole (eg, vomiting, hepatopathy, blood dyscrasia) cats should be re-evaluated at 2-week intervals while on a methimazole trial.

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UPDATE ON FELINE THYROID DISORDERS

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Feline hyperthyroidism was first described in 1979 and 1980 by investigators in NYC and Boston. (Peterson, 1979; Holzworth, 1980) The question at that time and since then has been: Is hyperthyroidism a new disease in cats? Based on epidemiologic and hospital-acquired data, the answer appears to be "yes." During a 14-year period from 1970 to 1984, an average of 1.9 cats per year were diagnosed with hyperthyroidism; however, it is now estimated that the incidence is as high as 2% of the feline population seen in tertiary care veterinary facilities. (Peterson, 1994; Edinboro, 2004) Since then, hyperthyroidism has become the most frequently diagnosed endocrinopathy in the cat with reports stemming from North America, Europe (especially the UK), New Zealand, and Australia. Hyperthyroidism is the most common endocrinopathy of cats and is caused by adenomatous hyperplasia of the thyroid gland. Middle-aged to older cats are typically affected, and there is no predilection for breed or sex, although some studies suggest a male predilection and a decreased incidence in Himalayans and Siamese (Kass, 1999).

Hyperthyroidism is characterized by hypermetabolism; therefore, polyphagia, weight loss, polydipsia, and polyuria are the most prominent features of the disease. Activation of the sympathetic nervous system is also seen; hyperactivity, tachycardia, pupillary dilatation, and behavioral changes are characteristic of the disease in cats. Long-standing hyperthyroidism leads to hypertrophic cardiomyopathy, high-output heart failure, and cachexia, which may lead to death. Feline hyperthyroidism is diagnosed through measurement of total tetraiodothyronine (TT_4); TT_3 measurement is generally noncontributory to a diagnosis. Because the disease has become more common and recognized in its early stages, free T4 ($FT_{4)}$ concentrations have been shown to be more diagnostic of early or "occult" hyperthyroidism. However, FT_4 concentrations should be interpreted in light of the TT_4 because nonthyroidal illness (chronic renal failure) can result in spurious elevations of FT_4 as well.

NUTRITIONAL ASPECTS OF HYPERTHYROIDISM

An inability to secrete adequate amounts of thyroid hormone often leads to the enlargement of the thyroid gland, a condition known as goiter. In many places in the world, this condition is, or has been, caused by a deficiency of iodine in the diet. This has largely been corrected through the use of iodized salt. Balanced pet foods provide sufficient iodine but vary widely in iodine content (Johnson, 1992). The effects of this variation have been theorized to be important in cats, but there is no data to support or refute the theory. Tartellin et al in 1992 showed an acute inverse relationship between FT4 and dietary iodine in cats fed low and high iodine diets for 2 weeks. However, a subsequent paper concluded that when the cats were fed low or high iodine diets for more than 5 months, no effect on serum TT4 or FT4 was seen (Kyle, 1992). Chronic changes in dietary iodide are associated with "adaptation" of the thyroid gland and therefore are unlikely to be the cause of feline hyperthyroidism. One study showed that feeding a low-iodine diet to cats with preexisting hyperthyroidism failed to affect high circulating thyroid hormone concentrations. (Peterson, 1994; Mooney, 2001)

Canned cat food has been implicated as a cause of feline hyperthyroidism in multiple epidemiological studies. (Kass, 1999; Martin, 2000; Edinboro, 2004) The suspected goitrogen is bisphenol-A-diglycidyl ether (BADGE), a substance used in making the liner of easy-open "pop-top" cans. It is suspected that this compound can leach into the foods and be consumed by cats. While this BADGE-based lining is generally considered safe and is used for foods for human consumption, cats may be more susceptible to toxic effects of this compound because they have a greatly reduced ability to detoxify it via hepatic glucuronidation. Bisphenol A also reduces triiodothyronine binding and causes increased TSH secretion resulting in hyperthyroidism and goiter in rats and some humans. While cat studies may not be available, rodent studies show a very high safety margin (Poole, 2004). It should be noted that epidemiological studies showing associations are not the same as cause and effect. Over 90% of cats in the US consume commercial pet foods as their primary nutritional source, and relatively few develop hyperthyroidism

MOLECULAR ASPECTS OF HYPERTHYROIDISM

More recently, investigators have honed in on the molecular aspects of feline hyperthyroidism. The disease in cats is more similar to toxic nodular goiter in humans and is characterized by autonomous growth of thyroid follicles. The pathogenesis of toxic nodular goiter is an abnormality in the signal transduction of the thyroid cell. The TSH receptor on the thyroid cells activated receptor-coupled guanosine triphosphate-binding proteins (G proteins). Uniquely, the thyroid cell proliferation and hormone production are both controlled by the TSH receptor-G-protein-cAMP signaling. Overexpression of stimulatory G proteins and underexpression of inhibitory G proteins have been demonstrated in some humans with toxic nodular goiter (Derwalht, 1995; Delmer, 1992). Mutations of the TSH receptor that result in the receptor remaining activated without ligand (ie, TSH) have also been reported in humans with toxic nodular goiter (Parma, 1997; Fuhrer, 1997; Holzapfel, 1997; Russo, 1996).

In hyperthyroid cats, the same abnormalities have been investigated and it appears that activation mutation of the TSH receptor may be part of the pathogenesis of feline hyperthyroidism in some cats (Peeters, 2002). Furthermore, abnormalities of G proteins, specifically significantly decreased G inhibitory protein expression has been described in tissues from hyperthyroid cats (Hammer, 2000).

ENVIRONMENTAL ASPECTS OF HYPERTHYROIDISM

In one study, the use of cat litter was associated with an increased risk of hyperthyroidism (Kass, 1999); however, there was no significant difference between different litter brands suggesting that the use of litter is simply a marker of cats that are kept indoors (Peterson and Ward, 2007). Indoor cats are likely to live longer and hence have a higher risk of developing hyperthyroidism. One recent report implicated brominated flame retardants (BFRs) as carcinogens/goitrogens possibly associated with feline hyperthyroidism (Dye, 20007). Coincidently, BFRs were introduced 30 years ago at the same time that feline hyperthyroidism emerged. Bromide, a halide, is an intriguing agent to implicate in feline hyperthyroidism because of the unique composition of thyroid hormones which contain the halide iodide. In this recent abstract, serum levels of lipid adjusted serum polybrominated diphenyl ethers (PBDE) levels were 10- to 400-fold higher than those found in human exposure. The authors theorized that these findings of high PBDE serum levels are in accord with the most consistently identified risk factor which is "indoor living." The authors also propose that cats are at increased risk because of meticulous grooming behavior and increased exposure to furniture and carpets. The small size of cats is also a possible risk factor for increased serum levels of PBDEs.

CONGENITAL HYPOTHYROIDISM

Congenital hypothyroidism, which occurs in approximately 1 in 4,000 births, is a relatively common endocrine disorder of human infants. In the cat, spontaneous hypothyroidism is more common in the congenital form than adult onset. Congenital hypothyroidism may be caused by aplasia or hypoplasia of the thyroid gland, thyroid ectopia, dyshormonogenesis, maternal goitrogen ingestion, maternal radoactive iodine treatment, iodine deficiency (endemic goiter), autoimmune thyroiditis, hypopituitarism, isolated thyrotropin deficiency, hypothalamic disease, or isolated TRH deficiency. Most cases of feline hypothyroidism in kittens have been the result of dysgensis; however, Jones et al reported a family of Abyssinian cats with familial dyshormonogenesis. Hypothyroidism as a result of TSH resistance has also been described in a family of Japanese cats. Most inherited forms of hypothyroidism are inherited as an autosomal recessive trait.

Because thyroid hormone secretion is essential for normal postnatal development of the nervous and skeletal systems, congenital hypothyroidism is characterized by disproportionate dwarfism, central and peripheral nervous system abnormalities, and mental deficiency. In addition, many of the signs of adult-onset hypothyroidism, such as lethargy, inappetence, constipation, dermatopathy, and hypothermia may be observed. Congenital hypothyroidism, regardless of cause, results in characteristic historical and physical examination features. Kitten and infants have a history of large birth weight (in babies this is the result of prolonged gestation) which is followed by aberrant and delayed growth. In kittens, the first signs of abnormal growth occur as early as 3 weeks after birth and abnormal body proportions are evident by 8 weeks of age. This is similar to human infants which are normal at birth but, if undiagnosed, exhibit characteristic signs by 6 to 8 weeks of age. Historical findings in hypothyroid kittens, such as lethargy, mental dullness, weak nursing, delayed dental eruption and abdominal distension are also observed in hypothyroid children.

Physical features of hypothyroid dwarfism in children include hypotonia, umbilical hernia, skin mottling, large anterior and posterior fontanels, macroglossia, hoarse cry, distended abdomen, dry skin, jaundice, pallor, slow deep tendon reflex, delayed dental eruption and hypothermia. In kittens with congenital hypothyroidism, hypotonia, macroglossia, distended abdomen, dry skin, delayed dental eruption and hypothermia have been described. In addition, because cats develop more rapidly and become weight bearing sooner than human infants, gait abnormalities and disproportionate dwarfism are prominent features of feline congenital hypothyroidism. Midface hypoplasia, broad nose, and a large protruding tongue are some of the sequelae of untreated hypothyroidism in man. Similar facial features, such as broad maxillas and macroglossia, have been observed in affected kittens. In man, delayed eruption of permanent teeth is observed in untreated congenitally hypothyroid individuals; delayed dental eruption is characteristic of hypothyroid kittens treated after 4 months of age. In humans and in cats, both macroglossia and effusions of the body cavities are the result of myxedematous fluid accumulation. Hypothyroid kittens often exhibit haircoat abnormalities including, retention of the puppy haircoat and thinning of the haircoat. Congenitally hypothyroid rats exhibit alterations in hair shaft morphology as a result of thyroid hormone deficiency during development.

Thyroid hormone is crucial for proper post-natal development of the nervous system. As a result, a significant number of properly treated and all untreated hypothyroid infants exhibit poor coordination and speech impediments later in life. Delayed treatment often results in low perceptual-motor, visual-spatial, and language scores in children with congenital hypothyroidism. If treatment is delayed beyond 4 to 6 months in human babies, intelligence is irreversibly affected and mental retardation may ensue. Mental retardation is also likely in hypothyroid kittens; however, no objective evidence of delayed intelligence is available to assess affected animals. Because the bulk of cerebellar development occurs postnatally, Purkinje cell growth is also significantly affected by congenital hypothyroidism.

Skeletal abnormalities such as delayed maturation and epiphyseal dysgenesis are the hallmark of congenital hypothyroidism. Delayed epiphyseal maturation is observed in the vertebral bodies and long bones of affected kittens. Epiphyseal dysgenesis, which is characterized by a ragged epiphysis with scattered foci of calcification, is observed in both humans and cats with untreated congenital hypothyroidism. Normal epiphyseal development proceeds from a single center; however, in hypothyroidism, thyroid deficiency leads the development of multiple epiphyseal centers each with its own calcification progression. Disorderly epiphyseal calcification leads to secondary arthropathies in children suffering from untreated congenital hypothyroidism.

Clinicopathologic features of congenital hypothyroidism include hypercholesterolemia, hypercalcemia, and mild anemia. Hypercholesterolemia develops in both congenital and adult-onset hypothyroidism because of decreased hepatic metabolism and decreased fecal excretion of cholesterol. Hypercalcemia secondary to congenital hypothyroidism is the result of decreased renal clearance and increased gastrointestinal absorption of calcium. Decreased thyroid hormone stimulation of erythropoetic precursors results in a mild normocytic, normochromic anemia in some puppies and kittens suffering from hypothyroidism.

Thyroxine is essential for the proper transcription, translation and secretion of growth hormone by pituitary somatotrophs. In humans, circulating GH concentrations are very high during the first few days after birth but rapidly decrease during the subsequent few weeks to levels just slightly above those in adults. Diagnosis of congenital hypothyroidism is based on clinical signs, supporting clinicopathology and thyroid function testing.

Kittens exhibit serum TT4 concentration two to five times greater than adult dogs. It is vital to remember that normal kittens aged 5 to 6 weeks, have serum total thyroxine (TT4) concentrations two to three times higher than normal adult cats. Therefore, a serum TT4 of 2.0 µg/dL, which is normal for an adult cat, would be low in a 6-week-old kitten and indicative of thyroid dysfunction. Serum free thyroxine (FT4) would also be expected to be higher in neonatal cats. In summary, congenital hypothyroidism is recognized by characteristic physical examination findings (dwarfism, delayed dental eruption, etc), clinicopathologic and radiological features and confirmed by thyroid function testing.

ADULT-ONSET HYPOTHYROIDISM

Spontaneous hypothyroidism secondary to lymphocytic thyroiditis has been described in one adult cat. However, the most common cause of adult-onset hypothyroidism in cats is iatrogenic following radioactive iodine therapy for hyperthyroidism. Clinical signs of hypothyroidism are gradual and subtle in onset, with lethargy and obesity being most commonly reported signs of hypothyroidism. The hypothyroid cat “slows down” gradually, and the owner may report gradual weight gain and lethargy. Interestingly, owners will often report that the animal is not hungry and may even have a reduced appetite despite weight gain. The owner may subject the cat to a severely calorie-restricted diet without success. Puffy facial features associated with myxedema and severe apathy was reported in a hypothyroid cat. The most common clinical symptoms of hypothyroidism in adult cats are lethargy, weight gain depression, hypothermia, and bardycardia.

Symmetric trunkal or tailhead alopecia is a classic finding in hypothyroid cats. The skin is often thickened because of myxedematous accumulations in the dermis. Hyperkeratosis, hyperpigmentation, secondary pyodermas and demidicosis are also observed as a result of defects in cutaneous immunity. Seborrhea, either sicca or oleosa, can be a clinical feature of canine hypothyroidism. Spontaneous or iatrogenic hypothyroidism following radioactive iodine treatment of hyperthyroidism in cats results in skin changes such a seborrhea sicca, poor hair regrowth after clipping and matting of the hair and trunkal alopecia.

Cardiovascular signs such as bradycardia, decreased cardiac contractility, and atherosclerosis are uncommon presenting complaints in hypothyroid animals. Neuropathies including bilateral or unilateral facial nerve paralysis, vestibular disease and lower motor neuron disorders are occasionally seen in hypothyroid dogs, but not reported in cats. In humans, carpal tunnel syndrome is often associated with hypothyroidism as a result of compression of the nerves from myxedema. Myxedema results in compression of the facial nerve as it exits the skull causing the classic “tragic” facial expression of hypothyroid cats. Myxedema coma is an unusual finding in hypothyroid dogs and cats manifests as stupor and coma secondary to myxedematous fluid accumulations in the brain and severe intracerebral hyponatremia.

Unusual ocular manifestations of hypothyroidism include corneal lipid deposits and lipemia retinalis. Keratoconjunctivitis sicca may occur in association with hypothyroidism. Gastrointestinal signs such as megaesophagus, reflux esophagitis, gastric atony, constipation and diarrhea, presumably due to small intestinal bacterial overgrowth caused by poor intestinal motility, are occasionally observed in hypothyroid animals.

Clinicopathologic findings such as normocytic normochromic anemia resulting from erythropoieitin deficiency, decreased bone marrow activity, and decreased serum iron and iron binding capacity would be expected to be observed in approximately 30% of hypothyroid cats. Hypercholesterolemia is seen in the majority of hypothyroid cats because of altered lipid metabolism and binding proteins (increased HDLs), decreased fecal excretion of cholesterol and decreased conversion of lipids to bile acids. Increased triglycerides are also seen in a smaller number of hypothyroid cats. Hyponatremia, a common finding in human beings with hypothyroidism, is observed as a mild decrease in serum sodium in hypothyroid animals. An unusual clinicopathologic feature of hypothyroidism is increased serum CPK possibly as a result of hypothyroid myopathy. Fructosamine concentrations can be affected in both hyperthyroid and hypothyroid individuals as a result of changes in clearance and protein turnover. Hypothyroid cats will exhibit increased serum fructosamine concentrations in the high end of the normal range. This slowed turnover of fructosamine may lead to falsely elevated serum fructosamine in cats with concurrent diabetes mellitus. In addition, impaired glucose tolerance has been observed in hypothyroid cats and humans as a result of altered lipids in the hypothyroid state. In the author's experience, sudden onset of diabetes mellitus or exacerbation of type 2 diabetes mellitus is observed in iatrogenically hypothyroid cats.

Diagnosis of hypothyroidism in cats may be based on measurement of serum basal total thyroxine (T4) and triiodothyronine (T3) concentrations, serum free T4 and T3 concentrations, endogenous canine serum TSH levels and response to therapy. Often, the combination of basal TT4 and endogenous TSH concentrations is the most economical and efficient way to diagnose hypothyroidism in cats. Measurement of serum total T3/T4 has been used as the mainstay of diagnosis in animals; however, the specificity of these tests leaves much to be desired. However, the specificity of a low T4 is much less accurate at approximately 70%. "Euthyroid-sick" syndrome is characterized by a decrease in serum TT4 and increase in reverse T3; tissue concentrations of T3 remain unchanged. Concurrent illnesses such as diabetes mellitus, CRF, hepatic insufficiency, and infections, and drugs such as anesthetics, phenobarbital, primidone, diazepam, trimethoprim-sulfa, quinidine, phenylbutazone, salicylates and glucocorticoids can also decrease serum basal TT4 concentrations. The more severe the illness, the lower the total T4 concentration.

Free T4 is the fraction of T4 unbound to protein and available for tissue uptake. The method used to measure FT4 is important with equilibrium dialysis being the method of choice. Using this technique, measurement is a two-step process, which takes longer to complete (24 to 48 hours) and is therefore more expensive. The first step involves the dialysis of the test sample across a membrane which is impermeable to protein bound T4. The second step is to subject the dialysate to an ultra sensitive T4 radioimmunoassay. Free thyroid hormone concentrations, or unbound thyroxine and triiodothyronine, are used in human medicine to differentiate between "euthyroid sick" syndrome and true hypothyroidism. Theoretically, FT4 is not subject to spontaneous or drug-induced changes that occur with TT4. The diagnostic accuracy of FT4 by dialysis is approximately 90%. Because of the expense and time involved in ordering a free T4 by dialysis, the author prefers to use TT4 and endogenous TSH concentrations as the first battery of tests. If confounding results are obtained, a free T4 by dialysis may be ordered to clarify the situation.

ENDOGENOUS cTSH CONCENTRATIONS

In human beings, when both endogenous TSH and TT4 concentration are increased and decreased respectively, diagnostic accuracy for primary hypothyroidism approaches 100%. In fact, endogenous TSH has become the "gold standard" for the diagnosis of hypothyroidism in human beings. As serum TT4 and FT4 concentrations decrease, intracellular T3 also decreases initiating a logarithmic increase in serum endogenous TSH concentration. This sensitivity to intracellular T3 makes eTSH the most sensitive test for the detection of early hypothyroidism. Although there is no feline specific TSH assay, the canine immunoradiometric assay may be useful in the diagnosis of spontaneous hypothyroidism in cats. Cats with primary hypothyroidism (lymphocytic thyroiditis, thyroid dysgenesis, dyshormonogenesis, etc.) would be expected to have elevated endogenous TSH concentrations.

Treatment should include use of a product that has proven efficacy in veterinary patients and an adequate dose [22–44 µg/kg/day once (44) or twice (22) daily]. The author uses TT4, and endogenous cTSH as first line diagnostics to determine if a cat is suffering from hypothyroidism. This combination of tests has been shown to have the highest specificity, sensitivity and lowest overall cost.

References are available from the author upon request.

FRUCTOSAMINE TESTING

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The fructosamine blood test is one of several different parameters that can be used to regulate the pet with diabetes mellitus. It is one of two tests that can measure glycated proteins in the blood which can provide important indirect information pertaining to blood glucose levels accumulated over a given period of time. The fructosamine assay is based on the ability of ketoamine-linked glucose residues on glycated serum proteins to reduce the dye nitroblue tetrazolium. The term *fructosamine* refers to the ketoamine product formed as a result of the nonenzymatic reaction between glucose and the amino group on the lysine residues of the protein. Since the reaction is irreversible, fructosamine concentrations depend on the duration and the extent of the hyperglycemia and the half-life of the serum proteins, thus providing an approximation of average blood glucose concentrations over a period of 1 to 3 weeks. The initial work by Reusch et al showed that the range in normal dogs is 187 to 386 µmol/L while concentrations in untreated diabetic dogs ranged from 325 to 834 µmol/L with some degree of overlap among the well controlled and poorly controlled groups.[1] According to Feldman and Nelson most diabetic dogs are reported to be doing well with a fructosamine range between 350 and 450 µmol/L with values greater than 500 suggesting inadequate diabetic control and values less than 300 reflecting prolonged hypoglycemia.

Reusch et al also showed that the fructosamine blood levels in normal cats ranged from 221 to 341 µmol/L with diabetic cats ranging from 226 to 835 µmol/L again with some overlap between groups. Crenshaw et al found that there was a good correlation between blood glucose levels and fructosamine blood levels in diabetic cats and that it was a meaningful test in distinguishing diabetes from stress hyperglycemia.[2] Feldman and Nelson show that well controlled diabetic cats have fructosamine values ranging from 350 to 450 µmol/L while those in poor control have average values exceeding 500 similar to dogs. A value of 300 µmol/L or less indicates prolonged hypoglycemia, again similar to dogs.

A possible pitfall with the serum fructosamine test is that a "well regulated range " can be the average level with any diabetic patient being considerably hyperglycemic for half of the treatment period and hypoglycemic during the other half. The patient's history should provide clues to such dysregulated periods of hyperglycemia such as signs of polydipsia and polyuria, and weight loss and any neurological abnormalities typical of hypoglycemia.

Dr. Deborah Greco has developed a very simple algorithm comparing the serum fructosamine (FR in µmol/L) blood concentration with a simultaneous blood glucose (BG in mg/dL) measurement taken at mid-day. This is a simple and very practical method of monitoring for both the veterinarian and the pet owner. The guidelines are as follows:

- FR < 400; BG < 180 = Excellent control
- FR > 400; BG < 180 = Poor owner compliance
- FR < 400; BG < 60 = Over regulation
- FR < 400; BG > 180 = Stress induced hyperglycemia*
- FR > 400; BG > 180 = Poor control

(*) Studies show that short-termed stress hyperglycemia does not increase the fructosamine blood level because the fructosamine concentration must maintain that increase for 4 or more days before it will be detected in elevated amounts.

A method by Dr. Ellen Behrend that is used to avoid confusion because of overlap values entails running a series of fructosamine blood levels in order to establish a trend over a period of weeks which will give a strong indication about the degree of diabetic control with repeated low values indicating excessive insulin use and with elevated values indicating inadequate insulin use.

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MONITORING THE FELINE DIABETIC

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Pet owners can use several different techniques to monitor their diabetic cats. Each technique offers certain advantages and disadvantages that are summarized below.

SPOT BLOOD GLUCOSE CHECKS

Advantages: Ease in having to collect one blood sample. Might reflect accurate patient status on the most stable diabetic.

Disadvantages: That particular sample might not reflect the varying blood glucose levels in that patient. The stress of the office visit and blood collection might give a falsely high result. Sample collection can be difficult in the fractious cat.

BLOOD GLUCOSE CURVES IN THE HOSPITAL

Advantages: Provides a more spread out time assessment of the cat's response to the insulin injection for a more accurate interpretation.

Disadvantages: Requires hospitalization for at least 8 hours. Numerous blood collections are required, which might be difficult to procure and expensive. Any stress caused by the hospitalization and the several phlebotomies can give falsely high levels. False results are possible if the cat does not eat. Inserting an indwelling venous catheter is costly and again an added initial stress to the cat.

BLOOD GLUCOSE CURVES AT HOME

Advantages: In an ideal world, this method can provide accurate serial blood glucose determinations provided that the cat is calm and the owner effective with the technique.

Disadvantages: Many cats will not tolerate the repeated skin pricks. Fibrosis will set into areas of skin that are repeatedly used. Requires owner commitment and cat cooperation, which can be difficult to attain. The process might not be able to be continued in the owner's absence.

SERUM FRUCTOSAMINE DETERMINATIONS

Advantages: One blood sample reflects the blood glucose over a 2- to 3-week time period. Easy technique with minimal stress to the patient and minimal cost to the client. Commonly used today.

Disadvantages: Reflects an average value over a period of time. A normal value might be inaccurate if cat is hypoglycemic half the time and hyperglycemic the other half. Conditions such as hypoproteinemia, azotemia, and hyperlipidemia can give erroneous results.

URINE GLUCOSE MONITORING

Advantages: Simple to do at home, no stress to the cat, inexpensive, can give "ball-park" impression of the status of the diabetic regulation. Two sample collections (one in the morning and the other in the mid-late afternoon) will increase the accuracy. It is time tested with good results in many cases. Sample collection is easy with gravel collection technique.

Disadvantages: Time of sample collection might not truly reflect on the insulin's action in that patient. It gives only a qualitative instead of a quantitative impression of the insulin effect. Sample collection can be difficult if waiting for a fresh catch.

CLINICAL SIGNS

Advantages: Easy to do, no equipment necessary. Anyone can observe.

Disadvantages: Can be inaccurate if owner is a poor observer and bad record keeper. Furry patients might not readily show weight gain and weight loss. Metabolic decompensation might not be detectable until late stage. Owner's noncompliance with feeding can be a large complicating factor.

So what is the ideal monitoring technique? This is a difficult if not impossible question to answer because each method has its own advantages and disadvantages. Each pet owner, cat, and veterinarian will find what works best in each particular situation.

ENDOCRINE EMERGENCIES

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DIABETIC KETOACIDOSIS

Diabetic ketoacidosis (DKA) is one of the most commonly encountered endocrine emergencies in small animal practice. DKA is typically seen in previously undiagnosed diabetics and less commonly occurs in patients that are on inadequate amounts of insulin. In patients currently receiving insulin, DKA is typically seen in those with a concurrent illness leading to insulin resistance. The pathogenesis of DKA is multifactorial; the four underlying causes include insulin deficiency, diabetogenic hormone excess (catecholamines, cortisol, glucagons, growth hormone), fasting, and dehydration. The interplay between these factors further antagonizes the situation.

Clinical Findings

Patients with DKA are divided into those that are "healthy" and those that are sick. Healthy DKAs only display clinical signs typical of diabetes (polyurian/polydipsia [PU/PD], polyphagia, weight loss) and present without a history of vomiting, anorexia, or lethargy. Typically these patients have only trace-to-small amounts of ketonuria noted. Healthy DKAs can be treated like uncomplicated diabetics.

Sick DKA patients have other systemic signs such as vomiting and lethargy. Physical exam findings may include depression, dehydration, weakness, tachypnea – this may progress to Kussmaul respiration (slow, deep breathing) due to acidosis and an acetone odor to the breath. It is not uncommon for patients in DKA to be presented semicomatose. These patients are true EMERGENCIES!!! Signs may reflect concurrent illnesses as well.

Diagnosis

DKA can be rapidly and easily diagnosed. The criteria for establishing this diagnosis include hyperglycemia, glucosuria, ketonuria, and metabolic acidosis. The presence of hyperglycemia which can be documented using a portable glucometer or point-of-care analyzer in combination with glucosuria and ketonuria (detected using urine reagent strips) in a patient with appropriate clinical signs is usually sufficient to establish the diagnosis and begin treatment. *Whenever you suspect that a patient may be suffering from DKA, you should immediately check urine for the presence of both glucose and ketones!* Metabolic acidosis can be documented by doing a venous or arterial blood gas. For the purpose of analyzing pH, a venous blood gas is sufficient. Normal pH is 7.35 to 7.45. Bicarbonate (tCO_2) is often included on biochemistry profiles and will be decreased in acidotic patients. A minimum database (complete blood count [CBC], biochemistry profile, complete urinalysis [UA] with culture) is crucial to thoroughly rule out any concurrent disorders such as pancreatitis. It may be difficult to initially assess renal function due to the presence of prerenal azotemia and an osmotic diuresis secondary to the glucosuria.

TREATMENT

Fluids and Electrolytes

Fluids are the most crucial aspect to treating DKA. Rehydration alone will lower blood glucose concentrations. It is often beneficial therefore to start patients on fluids for a few hours prior to giving insulin. Normal saline is typically considered to be the fluid of choice because patients suffering from DKA are most often whole-body sodium depleted. Dehydration should be corrected over 24 hours. Fluid therapy is critical in treating electrolyte imbalances. Most DKAs are moderately to severely hypokalemic. Their initial blood work may not reflect this deficit. In acidosis, K^+ often comes out of the cells as H+ ions move intracellularly, masking severe hypokalemia. As treatment begins to correct the acidosis, the serum K+ concentration will drop. Insulin also causes K^+ to move intracellularly. The initial hypokalemia stems from K^+ loss through urine and GI and decreased intake due to anorexia. $[K^+]$ should be monitored once to twice daily. The rate of supplementation will depend on measured values. If the initial K+ is within normal limits, add 20 to 40 mEq of K^+ to the fluids (½ as KCl, ½ as KPO_4). If it is elevated initially, make sure the patient is producing urine and reassess. If it is low, larger amounts of K^+ will need to be added. It may be important to calculate the maximum rate of K+ infusion (0.5 mEq/kg/hr) to avoid over-supplementing. Clinical signs of hypokalemia include weakness, ventral flexion of the head and neck, and ileus.

Phosphate moves similarly to K+. Patients in DKA are typically hypophosphatemic due to renal losses. Initial bloodwork may not reveal this as acidosis causes phosphate to move extracellularly. Hypophosphatemia can be life-threatening. If levels fall < 1.5 mg/dL (4.65 mmol/L), hemolytic anemia may develop. Phosphate should also be monitored once to twice daily. To calculate how much to supplement, you can use the formula: Phosphate supplementation = 0.01–0.03 mmol/kg/hr. However, it is easier to calculate the amount of K^+ needed and give ½ as KCl and ½ as KPO_4.

Acid-Base Status

Correcting hypoperfusion with appropriate fluid therapy is very beneficial for correcting the acidosis. Most patients won't require specific therapy for their acidosis. If the patient is extremely depressed and has a pH < 7.1 or a CO_2 < 12 mEq/L, bicarbonate therapy should be considered. Any efforts to change pH should be done slowly so as not to cause rapid alterations in the pH of the CSF. Dose: mEq bicarb = body weight (kg) x 0.4 x (12 – patient's bicarb) x 0.5. Give this over 6 hours and then reassess.

Insulin Therapy

Many clinicians use an intermittent intramuscular regime. Regular insulin is used because it has a rapid onset and a brief duration of effect. An initial dose of 0.2 U/kg IM is followed by subsequent doses of 0.1 U/kg IM every 2 hours. Blood glucose should not drop faster than 50 to 75 mg/dL/hr! (900–1350 mmol/L). Hyperglycemia typically resolves in 4 to 8 hours whereas it may take 1 to 2 days to resolve ketosis. Once the patient is eating and otherwise stable, switch to longer-acting insulin such as lente or NPH.

A constant low-dose intravenous infusion of insulin can also be done. To utilize this regime, calculate the patient's daily requirements (0.1 U/kg/hr) of regular insulin. Take a 250-mL bag of saline → remove 10 mL → add a day's worth of insulin. When this fluid is administered at 10 mL/hr, the patient will receive its insulin. As the blood glucose concentration drops, the rate of infusion can be lowered. *This route requires extremely close supervision.*

Blood Glucose and Dextrose

Blood Glucose	Insulin	Fluids	Next BG
> 300	0.1 U/kg IM CRI @ 10 mL/hr	No dextrose	1–2 hr
100-300*	0.1–0.5 U/kg IM/SQ CRI @ 5 mL/hr	2.5% dextrose	2–4 hr
< 100	None	5% dextrose	1 hr

The goal is to keep the BG in the 100 to 200 mg/dL (180–360 mmol/L) range. The dextrose in the fluids and the dose of insulin administered will have to be adjusted to achieve this. Patients usually need to have their BG checked every 2 hours and changes made accordingly.

As patients stabilize and begin eating on their own, the dose of insulin will need to be increased from 0.1 U/kg. Insulin given subcutaneously will have a longer duration.

HYPEROSMOLAR NONKETOTIC DIABETIC MELLITUS (HONKDM)

This is a less common complication of DM. It has a similar pathogenesis to DKA with a relative deficiency in insulin. For the hyperosmolar syndrome to develop, some functioning beta cells must still be producing insulin. The existence of some insulin prevents the formation of ketones. Excessive dehydration leads to a decrease in glomerular filtration rate (GFR), which leads to a decrease in glucose excretion. Hyperglycemia worsens and causes an increase in plasma osmolality. Increased plasma osmolality draws water out of cerebral neurons → obtundation → less water intake → vicious cycle.

HONKDM is characterized by:

1) Severe hyperglycemia (BG > 600 mg/dL or > 10800 mmol/L)
2) Hyperosmolarity > 350 mOsm/kg [2(Na + K) + 0.05(glucose) + 0.33(BUN)]
3) Dehydration
4) Lack of ketones.

These patients may still be acidotic despite their lack of ketones because 1) ß-hydroxybutyrate is a ketone which is not detected with urine strips (to detect, add a drop of H_2O_2 to the urine) and 2) lactic acidosis is the end product of anaerobic metabolism of glucose.

Clinical Findings

Patients typically are quite depressed, even comatose. The weakness may have been for several weeks prior to presentation.

Treatment

The treatment is similar to that for DKA. Imbalances must be corrected very slowly. Fluid therapy is typically either 0.9% NaCl or 0.45% NaCl. Caution must be exercised to not decrease osmolarity too quickly. Decrease it by ½ to 1 osmol/hour. The goal should be to correct dehydration over 36 hours. While patients may still be hypokalemic, this abnormality does not tend to be as severe as in DKA because they do not have as great of an osmotic diuresis. Patients with hyperosmolar diabetes may be hyperphosphatemic depending on the azotemia. Hypophosphatemia is less of a concern in HONKDM. Insulin therapy is the same as for DKA. These patients must be monitored very closely! Monitor urine output, electrolytes and renal values 1 to 3 times daily.

HYPOGLYCEMIA

Hypoglycemia is defined as BG < 60 mg/dL (1080 mmol/L). Symptoms of hypoglycemia include weakness, ataxia, seizures, and coma. While hypoglycemia results from another disorder that may require more definitive therapy, emergency treatment for hypoglycemia is often required. Common causes of hypoglycemia include lab error, liver disease, excessive insulin (iatrogenic or endogenous), decreased diabetogenic hormones such as cortisol, hypoglycemia of toy breed puppies, and "hunting dog" hypoglycemia. Other potential causes of hypoglycemia are pregnancy, glycogen storage diseases, non-insulin-secreting neoplasias, sepsis, uremia, starvation and severe polycythemia. Severe hypoglycemia (BG < 40 mg/dL) is most common with insulin-secreting tumors, portosystemic shunts and in toy breed puppies. The patient's signalment and history will often help distinguish among the different etiologies for hypoglycemia.

Patients symptomatic for hypoglycemia require some form of glucose supplementation. Patients who are ataxic but still mentally alert may be fed. Seizuring or comatose patients will need intravenous administration of dextrose. Dextrose should never be given in a concentration greater than 25% to prevent phlebitis. Caution has to be exercised in administering dextrose to patients with insulin-secreting tumors. These tumors tend to respond to glucose, therefore if the patient is bolused with dextrose, the tumor will dump more insulin and worsening hypoglycemia will ensue. Dogs that present seizuring are a therapeutic challenge. They need to be given enough dextrose to stop the seizures but hopefully not so much as to lead to further insulin release. Small frequent, high-fiber meals are a better route for providing more continuous glucose in patients that can eat. Some dogs will need to be given glucocorticoids to counteract the insulin.

HYPOADRENOCORTICAL CRISIS

The initial diagnosis of hypoadrenocorticism (Addison's disease) is frequently made for a patient presenting in crisis. For a patient to suffer from a full-blown Addisonian crisis usually involves the adrenal glands to not be producing either glucocorticoids or mineralocorticoids. Addisonians can present as emergencies in a variety of ways. Extreme lethargy or collapse often results from severe hypovolemia and an inability to deal with stress. Patients may also present for seizures secondary to hypoglycemia (due to the lack of glucocorticoids). Another possible emergent presentation for a dog suffering from an Addisonian crisis would be hemorrhagic gastroenteritis. In most cases, a detailed history will reveal previous, albeit subtle, symptoms of Addison's.

Diagnosis

Addison's disease often requires treatment be initiated prior to the diagnosis being fully established. In addition to the history, physical exam findings and initial laboratory data are often suggestive of this disease. For many Addisonians, the most noteworthy discovery may be the lack of abnormalities. Addisonians will lack the tachycardia appropriate for their clinical state of shock. A CBC will fail to reveal a stress leukon despite the patient being quite ill. Anemia can also be noted and may be fairly severe. Electrolyte changes (hyperkalemia and hyponatremia) due to mineralocorticoid deficiency are one of the classic findings in Addison's disease. Other disease processes can lead to these findings **and the electrolyte changes are NOT pathognomonic for Addison's!** A variety of changes can be seen on an EKG secondary to the hyperkalemia, including bradycardia, small or absent P waves, tall, tented t waves and wide QRS complexes. Azotemia is often seen due to the profound hypovolemia. Addison's disease and acute renal failure can present very similarly. Patients with Addison's disease may not be able to concentrate their urine appropriately secondary to medullary washout. Other changes that may be noted on initial bloodwork include hypoglycemia which can be quite severe, hypercalcemia, increased liver enzymes, hypoalbuminemia and metabolic acidosis. Radiographs may indicate hypovolemia (microcardia, small vessels). **The only test that definitively diagnoses Addison's disease is an ACTH stimulation test.**

Treatment

Fluids are the most crucial aspect to therapy for the crisis state. These patients are extremely hypovolemic. Patients who die from Addisonian crises die more from hypovolemic shock rather than hyperkalemia. Place 1 to 2 intravenous (IV) catheters and give fluids as needed. If the patients are truly in a crisis situation, they will need shock doses of fluids. Normal saline is the fluid of choice, but lactated Ringer's solution (LRS) or Normosol are also satisfactory. If the patient is hypoglycemic, they may need 5% dextrose added to their fluids. Once fluid therapy has been initiated, start an ACTH stimulation test. If the patient is critical, do not wait for test results before beginning glucocorticoid treatment. Dexamethasone SP is fast and should not cross-react with test results. Give an initial dose of 0.5–2.0 mg/kg IV.

Hyperkalemia will often resolve with fluid therapy. If the patient is suffering from severe cardiac arrhythmias, more immediate treatment may be required. There are three treatment options for hyperkalemia:

- **Insulin** will drive K^+ into the cell. The dog can be given 10% dextrose 4 to 10 mL/kg to cause the release of endogenous insulin. If this is unsuccessful, give 0.06 to 0.12 U/kg of regular insulin IV. If you administer insulin, give dextrose-containing fluids and make sure to monitor the BG levels
- **Bicarbonate** can also be given for the hyperkalemia. Patients may also be severely acidotic so bicarb may serve two purposes (typically though, the acidosis is mild and will resolve with fluid therapy). Give 25% of the calculated dose [0.4 x BW(kg) x base deficit] and reassess.
- **Calcium** is cardioprotective. Giving calcium will not lower K^+ but it will protect the myocardium while other therapeutics work to lower the K^+ levels. Calcium gluconate 10% 0.5 to 1.0 mg/kg IV over 10 to 20 minutes.

Mineralocorticoid deficiencies are initially treated with fluid therapy. Once the patient is stable, maintenance therapy will need to be instituted. Continue IV dexamethasone 0.01 to 0.05 mg/kg bid until the patient is eating and can be switched to oral medications. Most animals will begin showing improvement within hours. Patients who presented in a critical condition should be maintained on IV fluids for a minimum of 48 hours. Careful monitoring of hydration, ECG, electrolytes, renal values, and acid-base status are usually indicated for the first 48 to 72 hours.

HYPOCALCEMIA

Hypocalcemia may occur for a variety of reasons. Clinical signs and physical exam findings attributable to hypocalcemia include:

- Tetany–Ionized Ca stabilizes nerve cell membranes. When animals are hypocalcemic, the nervous system becomes progressively more excited. The nerve fibers begin discharging on their own and cause muscle contractions. The nervous system is the most susceptible system in the body to the effects of hypocalcemia.
- Other neuromuscular: generalized seizures, focal muscle twitches, muscle cramping/pain, ataxia, stiff gait; neurologic exam may be hard to complete.

- Cardiac abnormalities – Ca has both positive inotropic and chronotropic effects. Tachyarrythmias have been seen in primary hypoparathyroid dogs.
- Nervousness, aggressive behavior
- Intense facial rubbing
- Panting, weakness, inappetance
- PU/PD
- Vomiting and diarrhea

Differentials for hypocalcemia are varied and include primary hypoparathyroidism, renal failure, acute pancreatitis, eclampsia, malabsorption syndromes (GI), phosphate-containing enemas, ethylene glycol toxicity, lab error, vitamin D deficiency, transfusions, trauma, and neoplasia. In most cases, the cause for hypocalcemia can be elucidated from the history, physical examination, ± parathyroid hormone levels and ionized calcium measurements.

Primary hypoparathyroidism is an uncommon disorder in dogs and is rare in cats. It can occur at any age. Females may be more commonly affected. While these animals have very severe hypocalcemia, the onset of tetany is quite unpredictable. Many of these dogs appear to be in a latent phase where stress or excitement can provoke the tetanic contractions. This disorder can be mistaken for epilepsy if bloodwork is not checked. These patients usually do not have true seizures in that they do not lose consciousness.

Treatment of critical cases initially involves parenteral calcium. Ca gluconate 10% 1.0 to 1.5 mL/kg slow IV as needed to control tetany. Monitor an EKG while administering for VPCs or bradycardia. If these occur, discontinue the infusion until the problem resolves. The dose needed to control tetany can then be given SQ every 6 to 8 hours until the serum calcium normalizes. Dilute the Ca gluconate in equal parts saline. Ca chloride can also be used IV to control tetany at a dose of 5 to 15 mg/kg IV. **Do NOT give Ca Chloride SQ!** It will cause tissue sloughing. Once the patient has stabilized, oral calcium can be used as necessary. Primary hypoparathyroid patients will require lifelong supplementation. (Patients with self-limiting problems such as eclampsia will not need treatment once their underlying disease has resolved). Many formulations of oral Ca are available. Ca carbonate is frequently used because it is readily available as an OTC medication as an antacid (Tums). The dose of Ca varies from patient to patient. In general: Dogs 1.0 to 4.0 grams/day in divided doses. Cats: 0.5 to 1.0 grams/day in divided doses. Ca carbonate is 40% calcium; 1 gram yields 20 mEq of Ca. One extra strength Tums has 750 mg of calcium carbonate so it yields 300 mg of Ca (patients may be taking over 10 tablets a day). Vitamin D supplementation may also be necessary for chronic conditions such as primary hypoparathyroidism. Different formulations are available. Use those that are fairly rapid in onset and in dissolution of effect (if the patient becomes hypercalcemic, you want to be able to stop the medication and have the hypercalcemia go away quickly).

Dihydrotachysterol will raise Ca levels in 1 to 7 days. Initial dose of DHT: 0.02–0.03 mg/kg/day divided BID. After a few days, taper the dose to 0.01–0.02 mg/kg/day. Some patients may respond to the liquid formulation better than pills.

Calcitriol (1,25-dihydroxyvitamin D) has an onset of action of 1 to 4 days and a half-life < 1 day. Because this drug does not require renal activation, it can be given at physiologic doses as opposed to the pharmaceutical doses needed for DHT. Initial dose of calcitriol: 0.03 to 0.06 µg/kg/day. Regardless of the formulations used, very close monitoring is required. Calcium levels should initially be checked every few days for 1 week, then weekly for a few months, and then every few months for life.

HYPOTHYROIDISM: MYXEDEMA COMA

Myxedema coma is a rare presentation of severe hypothyroidism. The signalment for these dogs is similar to that for dogs presenting with less severe signs of hypothyroidism. Rottweilers may be at an increased risk for myxedema coma. In addition to the more typical complaints related to hypothyroidism such as haircoat changes, patients will also have histories including mental dullness, depression, inappetance, and weakness. Physical examination may reveal non-pitting edema of the skin and face, hypothermia, bradycardia, hypotension and hypoventilation. Patients suffering from myxedema can rapidly progress from being stuporous to comatose. Often dogs suffering from myxedema coma have a concurrent illness.

Myxedema is due to accumulation of mucopolysaccharides and hyaluronic acid in the dermis, which bind water resulting in increased thickness of skin. Myxedematous accumulations in the brain, along with hyponatremia, account for the neurologic changes. Hyponatremia is due to an increase in total body water resulting from decreased renal excretion and tissue retention.

Early recognition of this disorder is crucial. Recognizing myxedema helps differentiate this disorder from other metabolic and neuromuscular disorders. Biochemical findings may include low thyroid hormone concentrations, hypercholesterolemia, hypoglycemia, increased lactate, hypoxia/hypercarbia and hyponatremia. Systemic hypotension is usually found.

If this condition is suspected, treatment should be instituted immediately. It may be necessary to initiate treatment prior to documenting thyroid hormone concentrations. Treatment consists of thyroid hormone supplementation and supportive care. Due to unpredictable absorption of agents from the gastrointestinal tract, subcutaneous or intramuscular sites, intravenous administration of thyroid hormone is recommended (Levothyroxine 5 µg/kg q 12 hr). Appropriate supportive care may include fluid therapy (saline with dextrose), passive, slow rewarming and potentially assisted ventilation. Rewarming may increase oxygen requirements and exacerbate circulatory failure. Improvement is usually noted within 8 hours.

References are available from the author upon request.

ADDISON'S DISEASE: A TREATABLE DISEASE THAT IS EASY TO MISS

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PATHOPHYSIOLOGY

Primary hypoadrenocorticism results from destruction of the adrenal cortex. The most likely cause is immune-mediated. Infections and neoplasia can invade the adrenal cortex. These patients typically lack both glucocorticoids and mineralocorticoids. **Secondary hypoadrenocorticism** stems from decreased secretion of adrenocorticotropic hormone (ACTH) by the pituitary gland. The adrenals are not stimulated to secrete glucocorticoids. Mineralocorticoid levels remain normal because these are under the control of the renin-angiotensin system. This may also be seen with long-term administration of corticosteroids. The term **atypical hypoadrenocorticism** is used to describe primary hypoadrenocorticism that manifests only glucocorticoid deficiency. It is believed to result from a more gradual destruction of adrenal tissue with preservation of the ability to secrete mineralocorticoids. It can be challenging to distinguish between secondary and atypical hypoadrenocorticism.

Glucocorticoids affect almost every tissue in the body. They are essential in glucose metabolism and gluconeogenesis. They also affect the immune system and inflammatory responses. Signs of glucocorticoid deficiency are varied. Lethargy, weakness, and exercise intolerance are often noted in dogs with hypoadrenocorticism due to decreased glucocorticoid activity. Gastrointestinal disturbance such as anorexia, vomiting, and diarrhea also stem from glucocorticoid deficiency. Glucocorticoids are necessary for maintaining the health and integrity of the gastrointestinal (GI) mucosa. Given the important role of glucocorticoids in tolerating stress, patients who are deficient in these hormones cannot tolerate stress well. This often manifests clinically as a waxing-waning nature to the disease.

Mineralocorticoids are crucial to water and electrolyte balances. In the normal animal, a decrease in blood volume or an increase in serum potassium results in increased aldosterone. Hypovolemia triggers aldosterone release by activating the renin-angiotensin system. Hypovolemia also leads to the release of ADH. Aldosterone increases the renal reabsorption of Na^+ and the secretion of K^+. When they have a deficiency in aldosterone, patients accumulate K^+ and H^+. Patients will lose excessive amounts of sodium, chloride and water. Clinically, these changes will be manifest as weakness, polyuria-polydipsia, and potentially hypovolemia and cardiac disturbances.

CLINICAL FEATURES

Signalment

This disease is typically seen in dogs between 2 and 7 years of age. This is predominantly a disease of females with a ratio of 70:30 females to males. This signalment is consistent with the suspected immune-mediated etiology. Breeds in which hypoadrenocorticism is suspected to be hereditary include Standard Poodles, Leonbergers, and Nova Scotia duck tolling retrievers.

History

There are two distinct manners in which a dog with hypoadrencorticsm may present; chronic, waxing-waning disease or an acute Addisonian crisis.

- The clinical signs associated with hypoadrenocorticism are vague and typically chronic. Signs are often referable to the gastrointestinal tract such as anorexia, vomiting, weight loss, and diarrhea. Anorexia is noted in approximately 90% of the cases. Lethargy is also seen in almost every case. One third of the cases demonstrated a waxing-waning nature. Polyuria-polydipsia is seen less frequently. Hematochezia, hematemesis, and melena are also uncommonly noted. The GI ulceration results from hypoperfusion and lack of glucocorticoids.
- Cases may present as an acute Addisonian crisis. Clinical signs seen in these critical patients include collapse and seizures. Upon closer inspection, these patients often have a more chronic history.

Physical Examination

- Patients may appear completely normal.
- Patients may be weak, hypothermic, or dehydrated.
- More severe cases may demonstrate bradycardia and weak pulses.

Diagnostics

Complete blood count (CBC)

- Nonregenerative anemia that may be mild to severe. The anemia is the result of chronic disease and potentially GI bleeding.
- Lack of a stress leukogram (normal numbers of eosinophils and lymphocytes). These patients may be quite ill so the lack of this abnormality is noteworthy.

Chemistry Profile

- Hyponatremia
- Hyperkalemia
- Hypochloremia
- Azotemia - Prerenal due to hypovolemia and hypotension. Greater increases in BUN relative to creatinine.
- Urine specific gravity - May be concentrated or dilute. Most patients with prerenal azotemia will have concentrated urine (this is often how that is defined). In patients with hypoadrenocorticism, they will have impaired concentrating abilities due to

chronic hyponatremia which causes a loss of the renal concentration gradient "medullary wash-out".

- Hypoglycemia - This ranges from quite mild to severe enough to cause seizures.
- Hypercalcemia - The severity of the hypercalcemia correlates with the hyperkalemia. The mechanism is not known.
- Metabolic acidosis- impaired renal H$^+$ secretion
- Hypoalbuminemia
- Increased liver enzymes

Imaging

Thoracic radiographs:

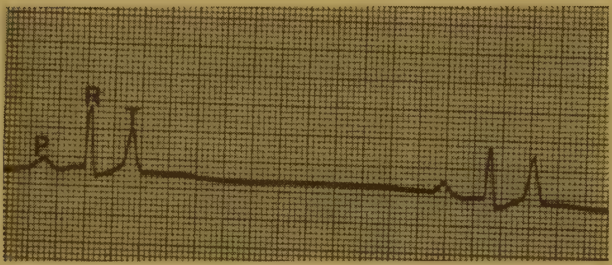
- Microcardia and small vena cava may be seen.
- Megaesophagus

Abdominal US or CT:

- Small adrenals may be noted

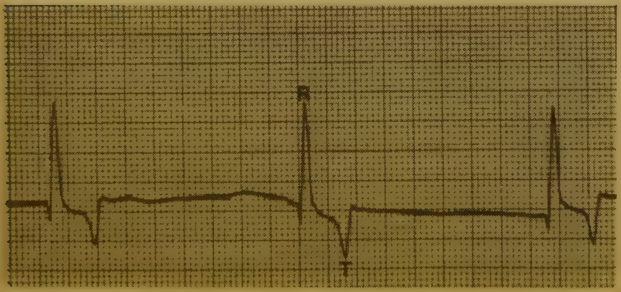
Electrocardiogram (ECG):

- K$^+$ = 5.5–6.5 mEq/L
    - Bradycardia
    - Tall, tented t waves:



- K$^+$ = 6.5–8.5 mEq/L
    - Decrease in R wave amplitude
    - Wide QRS
    - Prolonged P–R interval
    - Decreased P wave amplitude
    - Prolonged P wave duration

- K$^+$ > 7.5–8.5 mEq/L
    - Absence of P waves
    - ST deviation:



- K$^+$ > 11 mEq/L
    - Ventricular fibrillation or asystole

Blood pressure = Hypotension

DIAGNOSIS

The ACTH stimulation test (ACTH stim) is *the only way* to diagnose hypoadrenocorticism!!! Baseline cortisol or serum electrolytes serve to arouse suspicion for this disorder, not to confirm its presence. ACTH stim's are easy to run and interpret for hypoadrenocorticism.

Protocol

- Measure baseline cortisol
- Administer 5 µg/kg of Cortrosyn (synthetic ACTH) IV or IM. I prefer IV because there is not any concern for dehydration leading to delayed absorption.
- Measure post sample 1 hour following injection.
- Test interpretation: Dogs with primary, secondary or atypical hypoadrenocorticism will have abnormally low cortisols, both pre- and post-injection.
- *It is very important to get a complete medication history because prior administration of corticosteroids may suppress the hypophyseal-adrenocortical axis, causing the dog to be "flat-line" (no response to Cortrosyn administration).*

  Alternate protocol for ACTH stim using corticotropin (ACTH gel). This product is obtained from porcine pituitaries and currently has availability issues.
- Measure baseline cortisol
- Administer 2.2 U/kg of ACTH gel IM.
- Measure post sample 2 hours following injection.
    - The same normal ranges are used.

Other tests that may be of interest:

- Aldosterone levels can also be measured during the ACTH stim. These may help differentiate primary hypoadrenocortism from secondary.
- Endogenous ACTH levels may also help differentiate primary from secondary hypoadrenocorticism.

TREATMENT

Acute Crisis

- Fluids!!! These patients are extremely hypovolemic. Patients who die from Addisonian crises die more from hypovolemic shock rather than hyperkalemia. Place 1–2 IV catheters and give fluids as needed. If the patients are truly in a crisis situation, they will need shock doses of fluids. Normal saline is the fluid of choice, but LRS or Normosol are also satisfactory. If the patient is hypoglycemic, they may need 5% dextrose added to their fluids.
- Draw blood for electrolytes and start an ACTH stimulation test.
- Glucocorticoids. If the patient is critical, don't wait for test results before beginning treatment. Dexamethasone SP is fast and should not cross-react with test results. Give an initial dose of 0.5–1.0 mg/kg IV. Will need to switch to a maintenance protocol once the dog is eating.
- Hyperkalemia: there may be severe arrhythmias due to the electrolyte imbalances. Check an EKG

immediately. The fact that these patients come in shocky with a slow or normal heart rate is often the first indication of a serious abnormality! There may not be time to wait for blood tests to come back. If the EKG suggests severe hyperkalemia (bradycardia, no p waves, etc.), begin therapy.

  - Fluids are often enough to lower the hyperkalemia.
  - Insulin drives K^+ into the cell. Give 10% dextrose 4-10 mL/kg to cause release of endogenous insulin. If this is unsuccessful, give 0.06-0.12 U/kg of regular insulin IV. If you administer insulin, give dextrose-containing fluids and monitor blood glucose levels.
  - Bicarbonate can be given for the hyperkalemia. Patients may also be severely acidotic so bicarb may serve two purposes (typically though, the acidosis is mild and will resolve with fluid therapy). Give 25% of the calculated dose and reassess. 0.4 x BW (kg) x base deficit
  - Calcium is cardioprotective. Giving calcium will not lower the K^+ but it will protect the myocardium while other therapeutics lower the K^+ levels. Calcium gluconate 10% 0.5–1.0 mg/kg IV over 10–20 minutes.

- Mineralocorticoid supplementation can be started as soon as the patient is stable. See the recommendations for maintenance therapy.
- Correcting hypoperfusion with appropriate fluid therapy is very beneficial for correcting acidosis. Most patients will not require specific therapy for acidosis. If the patient is extremely depressed and has a pH < 7.1 or a CO_2 < 12 mEq/L, bicarbonate therapy should be considered.
  - mEq bicarb = body weight (kg) x 0.4 x (12 – patient's bicarb) x 0.25
  - Add this to the fluids so that the patient receives it over 6 hr
  - 0.4 corrects for the fact that bicarb is distributed in the extracellular fluid (ECF = 40% of body weight)
  - 0.25 is a correction factor to ensure that a conservative dose of bicarb is given
    - Reassess after 6 hours
- Most animals will begin improving within hours. Patients who present in a critical condition should be maintained on IV fluids for a minimum of 48 hours. Continue IV dexamethasone 0.01–0.05 mg/kg bid until the patient is eating and can be switched to oral medications.
- Monitoring:
  - Mm color, CRT, pulses
  - ECG q 4–6 hours or as needed
  - Electrolytes 2–4 times daily
  - Renal values may need monitoring if initially abnormal
  - Acid–base status

Maintenance Therapy

Primary hypoadrenocortical dogs will need to be supplemented with both mineralocorticoids and glucocorticoids for life. Dogs who are deficient in only glucocorticoids need to only have those supplemented; however, those dogs need to be monitored for their disease progressing to involve lack of mineralocorticoids as well. There are two options for **mineralocorticoid replacement**:

- DOCP (desoxycorticosterone pivalate) - The dose is 2 mg/kg IM or SQ q 25 days. Many dogs will require a slightly lower or less frequent dose (adjust based upon their electrolytes).
  - Initially recheck electrolytes at 12 and 25 days post injection for the first few injections. If sodium is low or potassium is high at day 12, increase the dose by 10%. If electrolytes are normal on day 12, but abnormal on day 25, decrease the dosing frequency by 48 hours. I have found that if their electrolytes are exceedingly normal at 25 days (not showing any tendency towards a low sodium or a high potassium), that I can extend the dosing period by 48 hours or more.
  - This drug contains very little glucocorticoid. Most dogs will also require prednisone.
- Florinef (fludrocortisone acetate) 0.01 mg/kg bid PO. This medication is supplied in 0.1 mg tablets so dogs may require 5 or 6 pills daily.
  - Initially recheck electrolytes weekly until patients are stable.
  - This medication contains glucocorticoids. Some dogs will actually show signs of glucocorticoid excess at the doses necessary to control their electrolyte imbalances.

Glucocorticoid replacement:

- Prednisone 0.1–0.2 mg/kg bid PO (physiologic dose) for primary and atypical hypoadrenocorticism.
- Dogs receiving Florinef may not need additional prednisone.
- In cases of iatrogenic hypoadrenocorticism (either Lysodren overdosage or withdrawal of chronic glucocorticoids), dogs will need to be tapered off steroids over a period of weeks. Watch for signs of weakness, GI disturbance. You may need to start with a dose higher than physiologic and taper down to that dose.
- During times of stress such as boarding, hunting, etc., dogs should have their glucocorticoid doses increased.

MONITORING

Addisonian dogs should have their electrolytes checked every 4 to 6 months for life. Some dogs will require higher doses of medication over time.

PROGNOSIS

Dogs with hypoadrenocorticism can have a normal lifespan with appropriate therapy!

References are available from the author upon request.

ORAL HYPOGLYCEMIC AGENTS IN DIABETES MELLITUS

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Oral medications can also be used, either in combination with insulin or in some cases, as sole agents (Table 1). Sulfonylureas such as **glipizide** and **glyburide** are insulin secretagogues. For these agents to be effective, the pancreas must be capable of producing insulin. These agents are typically used only in cats (diabetic dogs are rarely capable of producing insulin). There is concern that these drugs may cause the diabetes to progress if the underlying pathophysiology is pancreatic amyloidosis. Islet amyloid polypeptide (an amyloid precursor) is co-secreted with insulin so encouraging insulin secretion will lead to increased pre-amyloid secretion. Sulfonylureas may cause anorexia, vomiting, icterus, and an increase in liver enzymes. Glipizide is initially administered at a dose of 2.5 mg/cat twice daily; this dose can be increased to 5 mg/cat twice daily if the cat tolerates the medication and improved glycemic control is necessary. Glyburide is administered at a dose of 0.625 mg/cat once daily.

Other oral agents inhibit glucose absorption from the gastrointestinal tract. **Acarbose**, an α-glucosidase inhibitor, is an example of a drug in this class. This agent inhibits carbohydrate digestive enzymes in the gastrointestinal tract which delays carbohydrate absorption. Acarbose can be used in conjunction with insulin therapy in both dogs and cats. Use of acarbose may result in diarrhea. The recommended dose of Acarbose is 25–100 mg twice daily in dogs and 12.5–5 mg two to three times daily in cats. Acarbose should be given with food.

Agents that improve the sensitivity of peripheral tissues to insulin have also been examined. Two trace elements, **vanadium** and **chromium**, may have insulin-mimetic effects. While these agents do not raise serum levels of insulin, they may act at a post-receptor level to activate glucose metabolism within the cell. Vanadium mimics almost every action of insulin in skeletal muscle, adipose tissue and the liver. Studies examining the use of the agents in veterinary patients have had mixed results. Vanadium administration can result in anorexia and vomiting. Long-term administration of vanadium may result in toxicity due to accumulation in various tissues. One cat was observed to suffer from reversible acute renal failure after administration of vanadium for 1 year. The dose for vanadium in cats is 0.2 mg/kg once daily, mixed with food or water. Chromium is administered to cats at a dose of 200 µg/cat once daily; dogs receive 200–400 µg/dog once to twice daily. This trace element should also be given mixed with food or water.

Table 1. Oral Hypoglycemic Agents

	Dose	**Side Effects**
Agents that stimulate insulin secretion		
Glipizide	Cat: 2.5–5 mg q 12 hr	Anorexia, vomiting, icterus, increased liver enzymes
Glyburide	Cat: 0.625 mg q 24 hr	Anorexia, vomiting, icterus, increased liver enzymes
Agents that inhibit glucose absorption from the GI		
Acarbose	Cat: 12.5–25 mg q 8-12 hr. Give with food. Dog: 25–100 mg q 12 hr. Give with food.	Diarrhea
Insulin-Sensitizing Agents		
Vanadium	Cat: 0.2 mg/kg q 24 hr. Mix in food or water.	Anorexia, vomiting, possible renal failure
Chromium	Cat: 200 µg q 24 hr. Mix in food. Dog: 200-400 µg q 12–24 hr	Unknown
Troglitazone	Cat: 20-40 mg/kg q 12–24 hr	Hepatocellular injury, transient hemolysis
Metformin	Cat: 2 mg/kg q 12 hr	Nausea, diarrhea

Thiazolidinediones also enhance the sensitivity of peripheral tissues to insulin. This class of drugs includes **troglitazone** and **pioglitazone**. Troglitazone has been used as both a sole agent and in conjunction with insulin therapy. Due to human deaths secondary to hepatic failure, troglitazone has been withdrawn from the market. These agents need further evaluation in veterinary patients before they can be safely recommended.

The final group of drugs that augment insulin's actions are the biguanides. **Metformin** is the most commonly used member of this group. In addition to its effects on peripheral tissues, metformin also inhibits hepatic gluconeogenesis and glycogenolysis. Metformin can lead to gastrointestinal disturbances such as anorexia, vomiting and diarrhea. Patients with renal, hepatic or cardiac dysfunction should not receive metformin. More studies are needed to determine a potential role for metformin in treatment for veterinary diabetic patients. The dose in cats for metformin is 2 mg/kg twice daily.

References are available from the author upon request.

FELINE ENDOCRINE EMERGENCIES

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DIABETIC KETOACIDOSIS

Diabetic ketoacidosis (DKA) is one of the most commonly encountered endocrine emergencies in small animal practice. DKA is typically seen in previously undiagnosed diabetics and less commonly occurs in patients that are on inadequate amounts of insulin. In patients currently receiving insulin, DKA is typically seen in those with a concurrent illness leading to insulin resistance. The pathogenesis of DKA is multifactorial; the four underlying causes include insulin deficiency, diabetogenic hormone excess (catecholamines, cortisol, glucagons, growth hormone), fasting, and dehydration. The interplay between these factors further antagonizes the situation.

Clinical Findings

Patients with DKA are divided into those that are "healthy" and those that are sick. Healthy DKAs only display clinical signs typical of diabetes (polyuria/polydipsia [PU/PD], polyphagia, weight loss) and present without a history of vomiting, anorexia, or lethargy. Typically these patients have only trace-to-small amounts of ketonuria noted. Healthy DKAs can be treated like uncomplicated diabetics.

Sick DKA patients have other systemic signs such as vomiting and lethargy. Physical exam findings may include depression, dehydration, weakness, tachypnea—this may progress to Kussmaul respiration (slow, deep breathing) due to acidosis and an acetone odor to the breath. It is not uncommon for patients in DKA to be presented semicomatose. These patients are true EMERGENCIES!!! Signs may reflect concurrent illnesses as well.

Diagnosis

DKA can be rapidly and easily diagnosed. The criteria for establishing this diagnosis include hyperglycemia, glucosuria, ketonuria, and metabolic acidosis. The presence of hyperglycemia which can be documented using a portable glucometer or point-of-care analyzer in combination with glucosuria and ketonuria (detected using urine reagent strips) in a patient with appropriate clinical signs is usually sufficient to establish the diagnosis and begin treatment. *Whenever you suspect that a patient may be suffering from DKA, you should immediately check urine for the presence of both glucose and ketones!* Metabolic acidosis can be documented by doing a venous or arterial blood gas. For the purpose of analyzing pH, a venous blood gas is sufficient. Normal pH is 7.35 to 7.45. Bicarbonate (tCO_2) is often included on biochemistry profiles and will be decreased in acidotic patients. A minimum database (CBC, biochemistry profile, complete urinalysis with culture) is crucial to thoroughly rule out any concurrent disorders such as pancreatitis. It may be difficult to initially assess renal function due to the presence of prerenal azotemia and an osmotic diuresis secondary to the glucosuria.

TREATMENT

Fluids and Electrolytes

Fluids are the most crucial aspect to treating DKA. Rehydration alone will lower blood glucose concentrations. It is often beneficial therefore to start patients on fluids for a few hours prior to giving insulin. Normal saline is typically considered to be the fluid of choice because patients suffering from DKA are most often whole-body sodium depleted. Dehydration should be corrected over 24 hours. Fluid therapy is critical in treating electrolyte imbalances. Most DKAs are moderately to severely hypokalemic. Their initial blood work may not reflect this deficit. In acidosis, K^+ often comes out of the cells as H+ ions move intracellularly, masking severe hypokalemia. As treatment begins to correct the acidosis, the serum K+ concentration will drop. Insulin also causes K^+ to move intracellularly. The initial hypokalemia stems from K^+ loss through urine and GI and decreased intake due to anorexia. $[K^+]$ should be monitored once to twice daily. The rate of supplementation will depend on measured values. If the initial K+ is within normal limits, add 20 to 40 mEq of K^+ to the fluids (½ as KCl, ½ as KPO_4). If elevated initially, make sure the patient is producing urine and reassess. If it is low, larger amounts of K^+ will need to be added. It may be important to calculate the maximum rate of K+ infusion (0.5 mEq/kg/hr) to avoid over-supplementing. Clinical signs of hypokalemia include weakness, ventral flexion of the head and neck, and ileus.

Phosphate moves similarly to K+. Patients in DKA are typically hypophosphatemic due to renal losses. Initial bloodwork may not reveal this as acidosis causes phosphate to move extracellularly. Hypophosphatemia can be life-threatening. If levels fall below 1.5 mg/dL (4.65 mmol/L), hemolytic anemia may develop. Phosphate should also be monitored once to twice daily. To calculate how much to supplement, you can use the formula: Phosphate supplementation = 0.01–0.03 mmol/kg/hr. However, it is easier to calculate the amount of K^+ needed and give half as KCl and half as KPO_4.

Acid–Base Status

Correcting hypoperfusion with appropriate fluid therapy is very beneficial for correcting the acidosis. Most patients won't require specific therapy for their acidosis. If the patient is extremely depressed and has a pH < 7.1 or a $CO_2 < 12$ mEq/L, bicarbonate therapy should be considered. Any efforts to change pH should be done slowly so as not to cause rapid alterations in the pH of the CSF. Dose: mEq bicarb = body weight (kg) x 0.4 x (12 – patient's bicarb) x 0.5. Give this over 6 hours and then reassess.

Insulin Therapy

Many clinicians use an intermittent intramuscular regime. Regular insulin is used because it has a rapid onset and a brief duration of effect. An initial dose of 0.2 U/kg IM is followed by subsequent doses of 0.1 U/kg IM every 2 hours. Blood glucose should not drop faster than 50 to 75 mg/dl/hr! (900–1350 mmol/L). Hyperglycemia typically resolves in 4 to 8 hours whereas it may take 1 to 2 days to resolve ketosis. Once the patient is eating and otherwise stable, switch to longer acting insulin such as glargine or PZI.

A constant low-dose intravenous infusion of insulin can also be done. To utilize this regime, calculate the patient's daily requirements (0.1 U/kg/hr) of regular insulin. Take a 250 mL bag of saline, remove 10 mL, and add a days worth of insulin. When this fluid is administered at 10 mL/hr, the patient will receive its insulin. As the blood glucose concentration drops, the rate of infusion can be lowered. *This route requires extremely close supervision.*

Blood Glucose and Dextrose

The goal is to keep the blood glucose in the 100 to 200 mg/dL (180–360 mmol/L) range. The dextrose in the fluids and the dose of insulin administered will have to be adjusted to achieve this (Table 1). Patients usually need to have their blood glucose checked every 2 hours and changes made accordingly.

HYPEROSMOLAR NONKETOTIC DIABETIC MELLITUS (HONKDM)

This is a less common complication of diabetes mellitus; however, it is seen fairly often in cats. It has a similar pathogenesis to DKA with a relative deficiency in insulin. For the hyperosmolar syndrome to develop, some functioning beta cells must still be producing insulin. The existence of some insulin prevents the formation of ketones. Excessive dehydration leads to a decrease in GFR which leads to a decrease in glucose excretion. Hyperglycemia worsens and causes an increase in plasma osmolality. Increased plasma osmolality draws water out of cerebral neurons → obtundation → less water intake → vicious cycle.

HONKDM is characterized by:

1. Severe hyperglycemia (BG > 600 mg/dL or > 10800 mmol/L)
2. Hyperosmolarity > 350 mOsm/kg: $[2(Na + K) + 0.05(glucose) + 0.33(BUN)]$
3. Dehydration
4. Lack of ketones

These patients may still be acidotic despite their lack of ketones because 1) ß-hydroxybutyrate is a ketone which is not detected with urine strips (to detect, add a drop of H_2O_2 to the urine; and 2) lactic acidosis is the end product of anaerobic metabolism of glucose. One study of cats suffering from HONKDM found that the vast majority (90%) of cats suffered from an extremely serious, concurrent disease such as renal disease or heart failure.

Clinical Findings

Patients typically are quite depressed, even comatose. The weakness may have been for several weeks prior to presentation.

Treatment

Treatment of HONKDM is similar to that for DKA. Imbalances must be corrected **very slowly**. Fluid therapy is typically either 0.9% NaCl or 0.45% NaCl. Caution must be exercised to not decrease osmolarity too quickly. Decrease it by ½ to 1 osmol/hour. The goal should be to correct dehydration over 36 hours. While patients may still be hypokalemic, this abnormality does not tend to be as severe as in DKA because they do not have as great of an osmotic diuresis. Patients with hyperosmolar diabetes may be hyperphosphatemic depending on the azotemia. Hypophosphatemia is less of a concern in HONKDM. Insulin therapy is the same as for DKA. These patients must be monitored very closely! Monitor urine output, electrolytes and renal values one to three times daily. The prognosis for HONKDM is guarded, particularly if there is a serious concurrent disease.

HYPERTHYROIDISM

Thyroid Storm

Thyroid storm is a term used in human medicine to describe a life-threatening multisystemic disturbance due to elevated thyroid hormone levels. In humans, thyroid storm is usually associated with a precipitating event such as infection, surgery, or trauma. There are four main features to the clinical picture in humans: 1) fever, 2) tachycardia or supraventricular arrhythmias, 3) central nervous system symptoms, 4) gastrointestinal symptoms. Humans suffering from a "thyroid storm" have a very high mortality rate. It is currently debated whether feline patients suffer from a similar "thyroid storm". Certainly cats suffer from thyrotoxicosis (elevated thyroid hormone levels).

Table 1. Insulin Dose Adjustments According to to Blood Glucose Levels

Blood Glucose	Insulin	Fluids	Next Blood Glucose
> 300	0.2 U/kg IM CRI @ 10 mL/hr	No dextrose	1–2 hr
100–300*	0.1–0.5 U/kg IM/SQ CRI @ 5 mL/hr	2.5% Dextrose	2–4 hr
< 100	None	5% Dextrose	1 hr

*As patients stabilize and begin eating on their own, the dose of insulin will need to be increased from 0.1 U/kg. Insulin given subcutaneously will have a longer duration

Clinical Signs

Thyrotoxic cats may display a variety of clinical signs. Historically, owners may complain of polyphagia with weight loss, vomiting, diarrhea, polyuria/polydipsia, and behavior changes such as irritability. More emergent clinical signs include evidence of respiratory distress such as open-mouth breathing and tachypnea. The cat may be so stressed that he/she appears "panicked" and becomes extremely agitated with handling.

Physical examination typically reveals a palpably enlarged thyroid gland. A gallup rhythm or cardiac murmur is frequently auscultated. Many hyperthyroid cats suffer from cardiac hypertrophy. If the cat has progressed to heart failure, evidence of pulmonary edema such as crackles or pleural effusion such as dullness of the lung fields may be auscultated. Thyrotoxicosis may result in thromboembolic disease, often manifested in cats as a "saddle thrombus" with the cat presenting for acute paraplegia. Acute blindness secondary to retinal detachment due to systemic hypertension may be present. Severe hypokalemia or thiamine deficiency may result in muscle weakness and ventroflexion of the neck.

Treatment

It is critical to avoid stressing the cat as much as possible. If one is available, place the cat in an oxygen cage to provide supplemental oxygen. Most other ways of delivering supplemental oxygen such as nasal cannulas or face-mask are too stressful for these fragile cats. Cats displaying cardiac manifestations should be immediately treated with a beta-blocker such as atenolol (6.25–12.5 mg/cat/day) or propanolol (2.5–5 mg/cat q 8–12 hr or 0.02 mg/kg IV slowly). Production of thyroid hormone will need to be addressed. Methimazole (2.5–5 mg/cat q 12 hr) inhibits the organification of iodide, thus preventing the synthesis of new thyroid hormone. It may take up to a week however to see a decline in serum T4 levels. In critical cases, it may be necessary to block the secretion of already formed hormone. Iopanoic acid, a lipid-soluble radiographic contrast agent, blocks peripheral conversion of T4 to T3. The dose is 50 to 200 mg/cat BID PO. The systemic effects of thyrotoxicosis must also be addressed. Most of these cats will be hypovolemic so intravenous fluid therapy should be considered. Fluids will help treat pyrexia if that is a component of the presentation as well. Severe pyrexia may require additional cooling methods such as fans or cool water baths (if that doesn't excessively stress the cat). Potassium and vitamin B supplementation should be administered in cats displaying cervical ventroflexion. In humans suffering from "thyroid storm," glucocorticoids are recommended to decrease circulating hormone levels. The use of glucocorticoids has not been evaluated for this purpose in cats.

Blindness

Systemic hypertension may result from hyperthyroidism. Systemic hypertension may result in a variety of ophthalmic problems including retinal detachment, hemorrhage, or edema. It is important to consider hyperthyroidism as an underlying etiology in any cat that presents for acute blindness.

References are available from the author upon request.

UPDATE ON INSULIN THERAPY IN DOGS AND CATS

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PATHOPHYSIOLOGY OF DIABETES MELLITUS

Diabetes mellitus (DM) is a common endocrine disease in dogs and cats characterized by an absolute or relative deficiency of insulin. This results in a decreased ability of cells to take up and utilize not only glucose, but also amino acids, fatty acids, and electrolytes. In addition the lack of insulin results in increased gluconeogenesis, glycogenolysis, lipolysis, ketogenesis, and protein catabolism. Factors that have been identified as predisposing factors in cats include obesity, advancing age and being male. Burmese cats are also at increased risk. In dogs, older females are at higher risk of developing DM. Poodles, dachshunds, miniature pinschers, beagles, Golden retrievers, and miniature schnauzers are considered to be at higher risk than the general canine population. Keeshonden appear to have a genetic predisposition to the disease.

Two types of DM are recognized in humans, and these classifications can be applied to the disease in dogs and cats. Type I DM (insulin-dependent diabetes mellitus) is due to an absolute deficiency of insulin. This form of diabetes is characterized by minimal secretory response to beta-cell secretagogues such as glucagon, and is the most common form of diabetes recognized in the dog. Type II DM (non-insulin dependent diabetes) is characterized by abnormal insulin secretion and peripheral insulin resistance, and results in a stable reregulation of the blood glucose concentration at a higher concentration. This type of DM is rare in the dog but is more common in the cat. The two types of diabetes are classically distinguished by characteristic responses to challenge by insulin secretagogues such as glucose, glucagons, or arginine. In Type I DM, there is a decreased or negligible secretion of insulin compared to normal animals, whereas in Type II DM, total insulin secretion may be normal or increased, although the pattern of secretion may be abnormal. The insulin concentration is still insufficient, however, to prevent hyperglycemia. The phenomenon of glucose toxicity complicates interpretation of glucagon tolerance tests, particularly in cats, and the test is of little clinical utility. This limits our ability to definitively distinguish Type I from Type II diabetes mellitus in the cat.

DIAGNOSIS

The diagnosis of DM is made based on characteristic clinical signs of diabetes mellitus (polyuria, polydipsia, polyphagia, and weight loss), and documentation of hyperglycemia and glycosuria. In dogs the diagnosis is usually straight forward, however in cats it may be complicated by the occurrence of marked stress hyperglycemia. When making a diagnosis of DM in cats, it is therefore important not only to document persistent hyperglycemia and glycosuria, but also to rule out other diseases that may cause similar clinical signs. Measurement of fructosamine concentrations or glucose concentration in urine samples collected in the home environment may allow the clinician to distinguish between stress induced hyperglycemia (and resultant glycosuria) and persistent hyperglycemia due to diabetes mellitus. Glycosuria may also occur secondary to ketamine anesthesia, chronic renal failure, and post-obstructive diuresis. The presence of significant ketonuria together with hyperglycemia, is diagnostic for diabetes mellitus in both dogs and cats.

Cats are also unique in that DM may be transient or intermittent. Anywhere from 15% to 70% of newly diagnosed diabetic cats have been reported to go into spontaneous clinical remission with appropriate management. The variability from study to study probably arises from differences in the populations studied. The glucagon tolerance test is not useful in predicting whether or not a cat is likely to go into remission. Diabetes mellitus is usually permanent in dogs, unless DM occurs secondary to profound insulin resistance, due to hormones such as progestagens and glucocorticoids. This type of diabetes is sometimes referred to as Type III DM. If the diagnosis is made early and the cause of insulin resistance can be removed, the diabetes may also resolve.

INSULIN THERAPY

Classification of Insulin

It is very important for clinicians prescribing insulin to understand the various methods by which they are classified. Insulins may be classified by insulin source, insulin formulation, or duration of action of insulin. Not all forms of insulin are currently commercially available and product availability is likely to continue to change. Insulin formulations that are currently available include regular insulin (designated R), NPH insulin (designated N), Lente insulin (designated L), and PZI insulin. Insulins may be derived from bovine, porcine, or human recombinant sources and the concentration may be either 100 units/mL or 40 units/mL. A number of human recombinant insulin analogues are also available. Of these analogues, only glargine insulin has been extensively evaluated in veterinary patients.

Insulin Products Currently Available and Recommended for use in Dogs and Cats

- Short acting:
  - Regular insulin (Zinc insulin crystals)
    - Products: Humulin R [Lilly], Novolin R [NovoNordisk] Both human recombinant. 100 U/mL
- Moderate acting:
  - NPH insulin (neutral protamine hagedorn)
  - Complexed with protamine zinc in phosphate buffer
    - Products: (Humulin N [Lilly] , Novolin N [NovoNordisk] Both human recombinant 100 U/mL

  - Lente insulin (3 parts semilente, seven parts ultralente)
  - Mix of crystalline and amorphous in acetate buffer
    - Products: Vetsulin [Intervet] Pure pork insulin (40 U/mL)
- Long acting:
  - PZI insulin
  - Insulin complexed with protamine and zinc.
    - Products: PZI Vet, [Idexx] 90% Beef, 10% Pork (40 U/mL)
  - Glargine insulin
  - Long-acting analogue insulin
    - Products: Lantus insulin, Sanofi Aventis, human recombinant 100 U/mL
- Note that there is no longer a commercially available Ultralente insulin.

Insulin Therapy in Cats

Insulin products that are most suitable for use in cats include PZI and Glargine insulin. Lente insulin may also be used effectively in cats. PZI Vet in one study was effective in achieving glycemic control in 90% of diabetic cats. This insulin would be my first choice for use in cats; however, it is expensive. Preliminary studies of the long-acting insulin analogue (Glargine) have also been very promising, and this insulin is becoming the treatment of choice for many clinicians. As more data is accumulated on Glargine insulin it may well become the number one product for use in cats. Pork Lente insulin (Vetsulin) may also be used successfully in cats. Although it is not yet licensed in the US for cats, it has been used successfully for years in cats in Europe. Useful information regarding use of Vetsulin in cats (called Caninsulin in Europe) can be found at the Web site www.caninsulin.com. NPH insulin may also be used in the cat although it tends to have a very short duration of action and is therefore less likely to result in optimal glycemic control.

The starting dose for insulin in a new feline diabetic patient is 0.2–0.6 Unit/kg or 1–3 U/cat. It is recommended that PZI and Glargine insulins are started at the lower end of this dose.

It is difficult to predict in advance which cats will do better with which insulin formulation. The potency of different insulin formulations may vary from cat to cat, but this is not usually predictable in an individual animal, although longer-acting insulins as a rule are less potent than shorter acting insulin. It is therefore important that a blood glucose curve is performed within 5 to 7 days of making any change in insulin formulation. Cats should also be carefully monitored for clinical signs of hypoglycemia, because of the possibility of remission of diabetes mellitus in the cat. Whatever insulin formulation is chosen, twice a day insulin therapy is most likely to result in ideal glycemic control. If this is not possible, once a day therapy with PZI Vet or Glargine can often result in effective control of clinical signs, although diabetic remission may be less likely to occur.

Insulin Therapy in Dogs

Insulin formulations that are the most likely to result in good glycemic control in dogs include human recombinant NPH (Humulin N) or Lente (Vetinsulin®) insulin at a starting dose of 0.5 U/kg twice a day. Use of human recombinant insulin or pure pork insulin rather than beef containing insulins, appears to avoid the complications that can occur due to insulin antibodies in dogs treated with beef/pork insulin. Long-acting insulins such as PZI have an unpredictable duration in dogs and are not appropriate for the management of most diabetic dogs.

MONITORING OF RESPONSE TO INSULIN THERAPY

Adequacy of response to insulin therapy should be established by evaluation of clinical signs, measurement of blood and urine glucose concentrations (ideally a blood glucose curve) and measurement of serum fructosamine. After choosing the insulin dose, spot check blood glucoses may be measured for the last 24 to 48 hours of treatment. These should be used to detect hypoglycemia only. The insulin dose should not be increased base don these measurements. The first fullblood glucose curve should not be performed for at least 7 days after initiating treatment. There is significant day to day variation for the results of blood glucose curves and the results need to be interpreted in conjunction with the clinical signs. If hypoglycemia is detected the dose of insulin should be decreased. If hyperglycemia is detected on the blood glucose curve and this is in conjunction with persistent clinical signs of hyperglycemia, then the dose should be cautiously increased and the patient re-evaluated (usually in approximately 2 weeks). The clinician should not be in too much of hurry to achieve good glycemic control, because the risk of diabetic ketoacidosis decreases once insulin treatment has been initiated, and it can take a few weeks for the owner and the dog to settle into a good regime. In addition the phenomenon of glucose toxicity can delay the response to insulin. The target blood glucose nadir in diabetic dogs and cats should be between 100 and 200 mg/dL and ideally the blood glucose should be maintained between 100 and 300 mg/dL for the majority of the day. Once it appears that good glycemic control has been achieved measurement of a fructosamine concentration is useful to fine tune the insulin dose.

Switching from One Insulin Product to Another

The first step is to evaluate how well regulated the animal is on current insulin product and determine the potency of the new insulin versus old insulin (long-acting insulins are less potent than moderate-acting insulins). Then the frequency of administration of the new insulin should be determined. The new dose should then be based on a combination of these factors: If the animal has good glycemic regulation or if you are switching to a more potent insulin or increasing the frequency of administration then the dose should be decreased by 10% to 15%, if the patient does not currently have good glycemic control and the potency of the new insulin is the same or less, then use the same dose as before. Larger dose adjustments may be needed with changes in frequency of insulin administration. It is really important to confirm that the right dose choice was made by performing a blood glucose curve 7 to 10 days after the change is made. The new dose can then be adjusted as necessary.

Owners of diabetic dogs need to be educated about obtaining and using U40 insulin syringes if the patient is being switched to Vetsulin or PZI Vet. It is **NOT** recommended to use U100 syringes with U40 insulin by making a dose adjustment. This is liable to lead to serious errors.

Owners also need to be educated about the clinical signs of hypo- and hyperglycemia. They need to know what to do in the event of an episode of suspected hypoglycemia.

DIETARY MANAGEMENT

Dietary management is an important adjunct to insulin therapy in the management of diabetic dogs and cats. High-fiber, moderately fat-restricted diets are usually recommended for management of diabetic dogs. Exceptions to this are those patients for which palatability of these diets is an issue, those patients with other medical problems that might require a alternate prescription diet, and very debilitated patients in which more calorie-dense diets are necessary initially. There is less agreement about dietary management of diabetic cats. Options include a high-fiber, moderate-carbohydrate and low-fat diet; or a high-protein, low-carbohydrate diet; Which diet will be most effective in improving glycemic control in individual patients is unpredictable. Studies suggest that a high-protein, low-carbohydrate diet is more likely to result in diabetic remission in newly diagnosed diabetic cats.

POOR RESPONSE TO INSULIN

Clinical signs suggestive of inappropriate response to insulin therapy include recurrence or persistence of clinical signs of DM, disorientation or seizures due to hypoglycemia, or an insulin dose higher than 2 U/kg/dose in the dog or >6 U/dose in the cat. Adequate assessment of the cause of the problem requires performing a blood glucose curve. Measurement of glycosylated hemoglobin or fructosamine may also be helpful. Once the blood glucose curve has been obtained and interpreted, appropriate changes in treatment or further diagnostic testing can then be instituted. In dogs and cats receiving twice daily insulin, most glucose curves can be performed during working hours (8 AM to 6 PM). Common problems that may lead to a poor response to insulin include problems with owner administration, inappropriate insulin dose or formulation, insulin-induced hypoglycemia, rapid metabolism of insulin, and insulin resistance. When interpreting the results of blood glucose curves It is important to take into consideration the level of stress of the patient while in the hospital. Other factors such as clinical signs, results of urine blood glucose measurements at home, serum fructosamine concentrations, and changes in physical examination (especially body weight), should be taken into account when interpreting the results.

Problems with Owner Administration

Diagnosis of problems with owner administration of insulin sometimes requires administration of insulin from a new bottle in the clinic by a clinician or veterinary technician. Care should be taken to monitor the patient carefully in this setting however, because severe hypoglycemia can result if the insulin dose has been escalated due to problems with administration. If hypoglycemia does occur, the dose of administered insulin should be decreased by 25% to 75% and a blood glucose curve repeated after 7 days of the new dose.

Inappropriate Insulin Dose or Formulation

In most cases this diagnosis can be made easily by evaluation of the blood glucose curve. Most dogs and cats require insulin administration twice daily for good glycemic control, so this is the first change to consider if inadequate insulin dose is suspected.

Insulin-Induced Hypoglycemia

Insulin-induced hypoglycemia (Somogyi effect) occurs when excessive amounts of insulin are administered. When the blood glucose concentration drops below 65 mg/dL in response to insulin, compensatory mechanisms drive the blood glucose back into the normal range. These mechanisms include increased glycogenolysis, and gluconeogenesis by the liver, and release of catecholamines, glucagon, cortisol, and growth hormone which oppose the action of insulin. As the blood glucose returns toward normal however, there is not enough insulin present to oppose and dampen these mechanisms, and hyperglycemia may result. Since a spot-check blood glucose or urine measurement performed in the afternoon in such a case may reveal hyperglycemia and glycosuria, changes in insulin dosage based on these measurements may worsen the situation. The diagnosis of insulin-induced hypoglycemia is made by performing a blood glucose curve. The condition is treated by decreasing the insulin dose by 25% to 75% and reevaluation of a serial glucose curve 3 to 5 days later.

Rapid Metabolism of Insulin

Rapid metabolism of insulin refers to a situation in which the effect of insulin does not last as long as is necessary to control hyperglycemia for the majority of the treatment period. In most diabetic dogs and cats, twice daily insulin administration is necessary for ideal glycemic control. In some cases however the duration of effect may be only 5 to 8 hours. This may mean that hyperglycemia is present for a significant proportion of the day, even when twice daily administration is instituted. In most cases clinical signs of hyperglycemia are not present and no change to therapy is necessary. In some cases an insulin preparation with a longer duration may be necessary. Alternatively three times a day insulin treatment can be considered.

Insulin Resistance

There are many varied causes of true insulin resistance; however, most commonly it occurs due to the effect of excessive concentrations of hormones that oppose insulin. In many cases this is due to the presence of concurrent disease. The differential diagnosis of insulin resistance in dogs and cats is shown in Table 1.

Table 1. Insulin Resistance in Dogs and Cats (*Most Common)

Dogs	Cats
Drug administration (progestagens/corticosteroids)*	Drug administration (progestagens/corticosteroids)*
Infection (urinary tract/oral cavity/sepsis)*	Infection (urinary tract/oral cavity/sepsis)*
Hyperadrenocorticism*	Hyperthyroidism*
Hypothyroidism	Impaired insulin absorption (Ultralente insulin)
Renal disease*	Acromegaly*
Pancreatitis*	Pancreatitis*
Pregnancy/diestrus*	Renal disease*
Pheochromocytoma/glucagonoma	Hepatic disease
Hepatic disease	Cardiac insufficiency
Cardiac insufficiency	Hyperlipidemia
Hyperlipidemia*	Neoplasia
Neoplasia	Severe obesity*
Severe obesity*	Anti insulin antibody excess
Exocrine pancreatic insufficiency	Exocrine pancreatic insufficiency
Anti-insulin antibody excess (beef insulin)	Hyperadrenocorticism

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DIAGNOSTIC APPROACH TO HYPOGLYCEMIA IN THE DOG

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In the normal dog fasting does not usually result in hypoglycemia. Therefore a serum glucose concentration < 60 mg/dL is almost always due to either organic disease or to laboratory error. In an animal with normal glucose homeostasis, insulin secretion is stimulated when the blood glucose is > 110 mg/dL; insulin secretion is depressed and secretion of hormones that oppose insulin (epinephrine, glucagon, cortisol, growth hormone) is stimulated when the blood glucose falls below < 60 mg/dL.

Insulin acts by decreasing the rate of glycogenolysis and gluconeogenesis by the liver and increasing the rate of uptake of glucose by insulin sensitive tissues. In the presence of an insulinoma, neoplastic pancreatic beta cells continue to release insulin despite the presence of hypoglycemia. Clinical signs are dependent on the degree of hypoglycemia and the rate at which it develops.

EFFECT OF HYPOGLYCEMIA ON CNS

Glucose entrance into neurons is not insulin dependent (apart from the satiety and appetite centers in the hypothalamus). Decreased neuronal glucose concentrations cause inadequate ATP concentrations within the cell, resulting in increased vascular permeability, vasospasm, vascular dilatation, and edema. This causes neuronal death from anoxia. Histopathologic changes are most marked in the cerebral cortex, basal ganglion, hippocampus, and vasomotor cortex.

DIFFERENTIAL DIAGNOSIS OF HYPOGLYCEMIA

A wide range of disorders may result in hypoglycemia. The mechanisms causing hypoglycemia in these disorders is diverse, and may influence approach to treatment. Differential diagnosis of hypoglycemia in dogs and cats is shown in Table 1.

DIAGNOSIS OF HYPOGLYCEMIA

Diagnostic tests that are indicated to determine the cause of hypoglycemia include review of sample handling, and if necessary a repeat measurement to confirm the finding. A complete blood count is useful to evaluate for the presence of polycythemia, or leukocytosis, and may reflect evidence of sepsis. A serum biochemical panel may exhibit abnormalities consistent with hepatic disease or hypoadrenocorticism. Abdominal and thoracic radiographs may give support for neoplastic disease, while abdominal ultrasound is a useful screen for hepatic disease and smooth muscle tumors. Unfortunately, insulinomas are only detected via ultrasound in approximately 35% of dogs. Liver failure is evaluated by a liver function test such as measurement of bile acids, and hypoadrenocorticism is confirmed by a lack of an adequate cortisol response to ACTH administration. Diagnosis of insulinoma relies on paired measurement of serum insulin and glucose concentrations (see below).

EMERGENCY TREATMENT OF HYPOGLYCEMIA

Emergency management of hypoglycemia in the hospital setting relies predominantly on the intravenous administration of dextrose either as a bolus or constant rate infusion. A constant rate infusion of glucagon has also been shown to be useful in the emergency management of dogs with insulin-induced hypoglycemia. The appropriate starting dose for glucagon is 5 to 10 ng/kg/min. This is particularly effective in dogs with iatrogenic insulin overdose and in dogs with insulinoma.

Table 1. Differential Diagnosis of Hypoglycemia

Disorder	Mechanism of Hypoglycemia	Clinical signs (Y/N)
Hypoadrenocorticism	Cortisol deficiency	Yes
Liver disease, portovascular anomalies	Failure of gluconeogenesis, insufficient hepatic glycogen stores	Yes
Insulinoma	Insulin secretion from a neoplasm arising from beta cells of the pancreas	Yes
Other neoplasia	insulin-like factors, liver metastasis, glucose utilization by large tumors (hepatic tumors, leiomyoma, leiomyosarcoma)	Yes
Toy breed, puppy hypoglycemia	Alanine deficiency, limited hepatic glycogen stores, decreased muscle mass, lack adipose tissue, impaired gluconeogenesis	Yes
Sepsis	Hypoxic injury to hepatic cells, utilization of glucose by bacteria, increased tissue utilization glucose, other mechanisms	Yes
Artifactual hypoglycemia	Improper handling of samples	No
Glycogen storage disease	Hepatic enzyme deficiency	Yes
Polycythemia, high white blood cell counts	Increased utilization by red blood cells or white blood cells	No
Insulin overdose	Hyperinsulinism	Yes

INSULINOMA

Insulinomas are most common in middle-aged to older dogs. They have also been reported in aged cats. There is no sex predilection and a wide variety of breeds are affected. The clinical signs are typically episodic, since the effects of insulin on blood glucose are partially opposed by the action of diabetogenic hormones such as glucagon, cortisol, epinephrine, and growth hormone. Clinical signs are often precipitated by fasting, eating, exercise, or excitement, and include seizures, ataxia, weakness, collapse, muscle fasciculations, bizarre behavior, depression, nervousness, polyphagia and weight gain. Blood work is usually normal apart from hypoglycemia and increases in hepatic enzymes, which may be indicative of hepatic metastasis. The diagnosis relies on the measurement of normal or high serum insulin in the presence of a blood glucose concentration less than 60 mg/dL (normal 5–20 IU/mL). If the serum insulin is below detectable limits when the dog is hypoglycemic, the presence of an insulinoma is unlikely. If a borderline result is obtained a repeat measurement should be made. A number of ratios have been utilized to aid in the diagnosis of an insulinoma (eg, Insulin:glucose ratio, amended insulin:glucose ratio). The most commonly utilized index is the amended insulin;glucose ratio which is calculated by the following equation:

Amended insulin:glucose ratio =
plasma insulin(μU/mL)/(plasma glucose (mg/dL) – 30) x 100

The use of any insulin:glucose ratio is no longer recommended, however, because of a lack of specificity. In the case of non-diagnostic results, detection of an insulin peak is more likely if at least four glucose and insulin measurements are made during a 24-hour period.

Other provocative tests for diagnosis of insulinoma in dogs have also been evaluated (eg, glucagon, glucose, tolbutamide tolerance tests; epinephrine stimulation test). Unfortunately these tests are no more sensitive for making a diagnosis than concurrent measurement of insulin and glucose, and may potentiate hypoglycemia. Ultrasound may be useful in identifying the presence of a pancreatic mass; however, the sensitivity of ultrasound for diagnosis of insulinoma is only about 35% because tumors are often small or even microscopic. For this reason a normal ultrasound examination does not rule out insulinoma. Presurgical or intraoperative localization of insulinomas is important for effective surgical treatment. Because of their small size, insulinomas may be difficult to identify grossly or by palpation at surgery. The right and left lobes are involved with equal frequency and occult insulinomas are most common in the pancreatic body, therefore random partial pancreatectomy is controversial. Techniques for pre-surgical or intraoperative localization of insulinomas include administration of intravenous methylene blue, intraoperative ultrasound and scintigraphic techniques. Computed tomography, magnetic resonance imaging, and endoscopic ultrasound are additional techniques commonly used in humans for preoperative localization. CT has some utility in detection of small pancreatic tumors but has poor specificity for detection of metastatic disease in dogs with suspected insulinoma. Somatostatin receptor imaging may also be a useful adjunctive diangositc test for detection of insulinoma.

Surgical Resection of Tumor

Insulinomas in dogs and cats are malignant tumors and have a high predisposition to metastasize particularly to the lymph nodes, liver, and omentum. Metastatic disease is detected grossly in 30% to 50% cases at the time of surgery, and occult metastasis is present in most dogs. For this reason a cure is unlikely even in cases in which a single lesion is detected grossly. Removal of all gross tumor however, may allow clinical improvement and a good short-term prognosis. Long-term control of disease is only achieved in a small percentage of dogs. The goals of surgery for patients with insulinoma should be to confirm the disease, obtain tissue for histopathology, surgically remove all detectable gross disease if possible, and perform a complete exploratory laparotomy to detect evidence of metastasis. If suspected metastatic lesions are detected they should either be removed or a sample collected for histopathologic evaluation. In the approximately 20% of dogs in which the lesion is not grossly visible, one of the techniques for localization discussed above should be considered.

Complications after surgery include pancreatitis, diabetes mellitus, persistent hypoglycemia, and exocrine pancreatic insufficiency.

Medical Management of Insulinoma

Indications for medical management of insulinoma include stabilization of a patient prior to exploratory surgery, patients with obvious metastatic disease, and patients which have undergone surgery in which complete surgical removal of the tumor or metastases was not possible. In some cases frequent feeding of a diet high in fat, protein, and complex carbohydrates, but low in simple sugars will control clinical signs for a period of time. In addition, stress should be minimized and exercise limited. Once frequent feeding fails to control clinical signs, treatment with glucocorticoids is necessary. The starting dose for prednisone is 0.25 mg/kg every 12 hours. The dose should be titrated upward in order to control clinical signs as necessary. There is little benefit to increasing the dose above 3 mg/kg/dose. The drug diazoxide inhibits insulin secretion from the pancreas, stimulates gluconeogenesis and glycogenolysis, and has a direct inhibitory effect on cellular uptake of glucose. The recommended dose is 5 to 30 mg/kg every 12 hours. Again the recommendation is to start with the lowest dose and titrate upwards to effect. Side effects that have been reported include anorexia, vomiting, diarrhea, tachycardia, bone marrow suppression, and pancreatitis. Thiazide diuretics potentiate the effects of diazoxide. The recommended starting dose for hydrochlorothiazide is 2 to 4 mg/kg/day. In some cases routine medical therapy is not adequate to stabilize a patient adequately prior to surgery. In these cases intravenous glucagon infusion should be considered for short-term management of hypoglycemia. The somatostatin analogue octreotide has also been used in a small number of dogs with insulinoma. The drug works by stimulating somatostatin receptors in the pancreas which inhibit insulin synthesis and secretion. Octreotide at a dose of 10 to 40 µg SC every 8 to 12 hours is effective in approximately 50% of dogs; however, the drug is expensive and most dogs became refractory over time. Chemotherapeutic agents such as alloxan and streptozotocin have direct toxicity for the beta cells of the pancreas. Use of these drugs in dogs with insulinoma has been reported to cause partial or complete remission in 30% to 50% of dogs; however, nephrotoxicity of these drugs is high. In a recent study of 17 dogs with insulinoma treated with streptozocin and a diuresis protocol however, azotemia was only reported in one dog. Median duration of normoglycemia was 163 days. Two dogs had rapid resolution of paraneoplastic peripheral neuropathy and two others had measurable reductions in tumor size. Two dogs developed diabetes mellitus.

The long-term prognosis for insulinoma is poor. Survival times are generally longer for those dogs treated surgically. In one study, median survival for dogs treated surgically was 381 days (range 20–1758), while survival for those dogs treated medically was 74 days (range 8–508). However, dogs in the medical group tended to receive less aggressive therapy overall. The long-term prognosis for dogs with detectable metastatic disease is generally considered poor; however, long survival times after aggressive surgical debulking of primary and metastatic nodules has been reported. In one study of 28 dogs with insulinoma median survival time was 785 days. Nineteen of the dogs were treated with partial pancreatectomy and medical treatment with prednisone and diazoxide was initiated in those dogs that relapsed after surgery.

TREATMENT OF HYPOGLYCEMIA DUE TO OTHER CAUSES

In most other causes of hypoglycemia, treatment relies on short-term IV infusion of dextrose in addition to treatment of the underlying disease or condition. Glucagon infusion may be useful in dogs with insulin overdose. In cases of artifactual hypoglycemia, specific treatment of hypoglycemia is unnecessary.

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MANAGEMENT OF DIABETIC KETOACIDOSIS

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PATHOPHYSIOLOGY

Diabetes mellitus (DM) is a common endocrine disease in dogs and cats characterized by an absolute or relative deficiency of insulin. This results in a decreased ability of cells to take up and utilize not only glucose, but also amino acids, fatty acids, and electrolytes. In addition, the lack of insulin results in increased gluconeogenesis, glycogenolysis, lipolysis, ketogenesis, and protein catabolism.

If a diabetic dog or cat is not treated or receives inadequate insulin therapy, it will eventually become ketoacidotic. Some apparently well-controlled diabetic patients may also become ketoacidotic because of stress, illness, or estrus. The metabolic derangements that occur in diabetic ketoacidosis (DKA) are similar but more severe than those that occur in the uncomplicated diabetic. Factors that are thought to predispose to the development of DKA, in addition to lack of insulin, include excess diabetogenic hormones (in particular hyperglucagonemia), fasting, and dehydration. Hyperglucagonemia is currently thought to be primarily responsible for ketonemia. The combination of insulin deficiency and glucagon excess stimulates peripheral lipolysis, resulting in increased plasma fatty acid concentrations. Plasma fatty acids are normally converted to acetyl coenzyme A by the liver which is then converted into triglycerides or shunted into the citric acid cycle for production of protein, glucose or glycogen. In the presence of high glucagons concentratons, fatty acids are converted to acetoacetyl coenzyme A, which in turn is converted to acetoacetic acid. Acetoacetic acid may then be converted to acetone and betahydroxybutyric acid. Ketones are metabolized by many tissues and can serve as a short-term source of energy; however, production in excess of utilization results in metabolic acidosis and osmotic diuresis due to ketonuria. Dehydration, electrolyte depletion, vomition and diarrhea then follow. Prerenal azotemia and hyperosmolality may be further complications. These derangements are progressive and will eventually result in death if not treated.

Other diabetogenic hormones such as growth hormone and glucocorticoids also predispose to ketoacidosis. The secretion of these hormones may be increased by infection, fasting and other disease states. Dehydration will potentiate the effects of other disease states since this causes a decrease in glomerular filtration rate (GFR) and a loss of the ability to excrete glucose or hydrogen ions.

SIGNALMENT AND CLINICAL SIGNS OF KETOACIDOSIS

Because DKA is most commonly associated with a new diagnosis of diabetes mellitus (DM), the signalment for dogs and cats with DKA is similar to that for other presentations of DM. In a study of 104 newly diagnosed diabetic cats, ketoacidosis was present in 40% of cats. In another study of 221 diabetic dogs, 15% were diagnosed with diabetic ketoacidois. In one study of 42 cats with ketosis or ketoacidosis, diabetes mellitus was newly diagnosed in 26 cats, and previously diagnosed in 16 cats. Historical findings may include a classic prior history for diabetes mellitus, and often a history of recent concurrent disease such as bacterial infection. In two studies of diabetic ketoacidosis in dogs and cats, concurrent disease was identified in 71% of dogs, and 93% of cats. The time interval from initial clinical signs to development of DKA is very variable and ranged from 2 to 52 weeks in one study; however once clinical signs of ketoacidosis begin, severe illness occurs quite rapidly. In the study of ketoacidotic cats, the median time from development of systemic signs to hospitalization was 2 days (range 1–14). Severe DKA is characterized by fairly rapid onset of lethargy, anorexia, adipsia, vomiting, and diarrhea. Other historical findings may also be present depending on the presence of concurrent disease. Physical examination may reveal depression, dehydration, weakness, tachypnea, abdominal pain and sometimes an odor of acetone on the breath. A thorough physical examination is very important not only to establish severity of ketoacidosis but also because of the high incidence of concurrent diseases in these patients. In one study of concurrent disorders in dogs with diabetes mellitus, 21% had urinary tract infections, 23% had hyperadrenocorticism, 13% had acute pancreatitis, 5% had neoplasia and 4% were hypothyroid. Acidosis was detected in 46% of dogs and ketosis was documented in 15%. Concurrent diseases common in ketoacidotic cats include hepatic lipidosis, cholangiohepatitis, chronic renal failure, infection, neoplasia, and pancreatitis. The prognosis for animals with diabetic ketoacidosis often depends upon the severity and appropriate treatment of underlying disease.

LABORATORY ABNOMALITIES

The minimum database for a dog with suspected DKA should include a urinalysis and urine culture, CBC (or packed cell volume [PCV], total protein, white blood count [WBC] estimate), blood glucose, blood urea nitrogen (BUN), creatinine, electrolytes (sodium, potassium, chloride, phosphorus), and total CO_2 (+/- blood gas). Other diagnostic testing is dependent on the history and physical examination. The CBC may reveal leukocytosis or hemoconcentration, and the blood glucose may be as high as 1000 mg/dL depending on the severity of the volume depletion and decreased GFR. BUN and creatinine are commonly increased due to pre-renal azotemia or concurrent renal disease. Hyper- or hyponatremia may occur although hyponatremia is more common due to hyperosmolality (dilution), and loss of sodium in the urine by osmotic diuresis. Overall body stores of potassium are usually depleted in DKA but the measured serum potassium is usually normal or increased due to metabolic acidosis, lack of insulin, and hyperosmolality, all of which tend to tend to drive potassium extracellularly. Treatment of DKA will drive potassium back into cells and profound hypokalemia may therefore occur during treatment. Severe hypokalemia may be life threatening and requires immediate treatment. Some diabetic patients may be truly hyperkalemic due to concurrent acute renal failure or Addison's disease. Hypophosphatemia may also occur in DKA and is also exacerbated by insulin therapy. Hypophosphatemia may cause confusion, seizures, decreased myocardial contractility, respiratory failure, and hemolytic anemia, and requires immediate treatment. Hypomagnesemia has been reported in cats with diabetes mellitus; however, the clinical significance of this finding is unclear at this time. In one study of cats with a variety of disorders, hypomagnesemia was associated with increased morbidity and mortality.

A urinalysis will confirm the presence of glucose and ketones. Urine should also be evaluated for the presence of inflammatory sediment and a sample should be submitted for bacterial culture. The specific gravity will allow differentiation of renal from prerenal causes of azotemia, although high concentrations of glucose and ketones in the urine increase the specific gravity.

Serum osmolality may be increased in patients with severe DKA and correlates well with the level of consciousness. Osmolality is not commonly directly measured but can be calculated from the following formula.

$$\text{Osmolality} = 2\,(\text{Na}+\text{K}) + 0.05\,(\text{Glucose}) + 0.33\,(\text{BUN})$$

(where Na and K are measured in mEq/L and glucose and BUN are measured in mg/dL)

The average dog with DKA is not hyperosmolar because of concurrent hyponatremia; however, some individuals do have life-threatening hyperosmolality (> 350 mg/dL) and the careful use of hypotonic fluids (0.45% saline) may be required. Some nonketotic diabetic patients may also develop severe hyperosmolality.

Hyperosmolar Nonketotic Diabetes Mellitus

This is an unusual complication of DM characterized by severe hyperglycemia, hyperosmolality, and azotemia, with minimal ketosis or acidosis. The pathogenesis is similar to that for the uncomplicated diabetic, except that the osmolality becomes so high that it results in depressed CNS function. Lethargy, depression, and impaired water consumption then lead to severe vascular volume contraction, and azotemia, which worsens the hyperglycemia and hyperosmolality. The lack of ketonuria is not well understood. Clinically these dogs present with severe dehydration, depression, weakness, and shock.

TREATMENT HEALTHY KETOACIDOTIC PATIENT

In some dogs with mild DKA clinical signs are mild or absent and metabolic acidosis is mild. In these dogs aggressive therapy is not necessary; however, regular rather than long-acting insulin should be administered because of its increased potency. Insulin should be administered subcutaneously (SC) every 8 hours with a meal (1/3 caloric requirements) until ketonuria resolves. At this point longer-acting insulin treatment can be initiated.

TREATMENT OF SEVERE KETOACIDOSIS

The goals of therapy in DKA are to;

1. Restore water and electrolyte losses
2. Provide insulin and a carbohydrate substrate
3. Correct acidosis
4. Identify and treat precipitating causes and concurrent disease

Fluid Therapy

Fluid therapy should be started as soon as possible after presentation, preferably via a jugular catheter. The fluid rate should be calculated based on an estimate of dehydration, presence of ongoing losses and a maintenance rate that accounts for persistence of osmotic diuresis. In most cases the fluid of choice is normal saline with potassium, phosphorus, and dextrose supplementation as necessary. Hydration status should be monitored frequently (every 8 hours) and fluid rate adjusted accordingly. Response to fluid therapy should be assessed by clinical response, central venous pressure, bodyweight and urine output. It may be necessary to change to 0.45% saline if hyperosmolality (>350 mOsmol/L) is present, however this should only be done with extreme caution. Patients should also be monitored carefully for the development of pulmonary or cerebral edema.

The amount of potassium added to the fluids depends upon the serum K concentration; however, the total hourly K administration should not exceed 0.5 mEq/kg body weight.

Serum K (mEq/L)	MEq K Supplementation/ Liter Fluids
>3.5	20
3.0–3.5	30
2.5–3.0	40
2.0–2.5	6
<2.0	80

Phosphorus supplementation (potassium phosphate) is indicated if serum P decreases < 1.5 mg/dL or if clinical signs of hemolysis are detected. The dosage is 0.01 to 0.03 mmol/kg body weight per hour administered in calcium free fluids. Addition of 50% of the potassium requirement as potassium phosphate may result in oversupplementation and signs of hypocalcemia. Addition of potassium phosphate to the fluids does not always prevent development of hypophosphatemia, and patients should still be monitored for complications of hypophosphatemia such as hemolytic anemia.

Insulin Therapy

Over-aggressive therapy that results in rapid changes in blood glucose, osmolality, potassium or phosphorus concentrations or acid base balance should be avoided. The ideal mode of treatment is to administer small doses of regular insulin, frequently. The aim is to slowly decrease the blood glucose to 150 to 250 mg/dL over about 8 hours. Ketosis can take up to 48 hours to resolve. Low-dose insulin therapy accomplishes the goals of therapy without the risks of correcting hyperglycemia too quickly. Insulin may be administered either intramuscularly or intravenously. If using the IM protocol, insulin is administered at an initial loading dose of 0.2 U/kg, then at a dose of 0.1 U/kg hourly. The blood glucose should be monitored every hour prior to the next dose of insulin and should ideally decrease by no more than 50 to 100 mg/dL per hour. Once the blood glucose drops to <250 mg/dL the frequency of insulin administration can be decreased to every 4 to 6 hours IM or SC if hydration is adequate (dose 0.1 to 0.4 U/kg with adjustments based on blood glucose). For the IV protocol, insulin should be given at an initial rate of 2.2 U/kg/24 hours diluted in 250 mL 0.9% saline and administered through a separate line with an infusion or syringe pump at an initial rate of 10 mL//hour. The rate is then adjusted based on hourly measurements of blood glucose. Once the blood glucose drops below 250 mg/dL the insulin can then be administered SC as described above. Dextrose (5%) should be added to the fluids to decrease the risk of hypoglycemia, once the blood glucose decreases below 250 mg/dL. Longer-acting insulin should not be instituted until the patient is bright and alert, eating, and ketosis has resolved. In one study using an intravenous insulin protocol, ketonuria resolved within 6 to 72 hours.

Bicarbonate Therapy

Specific treatment of metabolic acidosis is usually not necessary since treatment of the underlying cause (ketonemia) will resolve the acidosis and in addition ketones will be metabolized to bicarbonate. In addition, paradoxical CNS acidosis, metabolic alkalosis, and decreased oxygen delivery to tissues are potential complication of bicarbonate administration. If the serum bicarbonate concentration falls below 10 mEq/L, or the pH. is less than 7.15, specific treatment with sodium bicarbonate is necessary since this degree of acidosis causes insulin resistance and can itself be life threatening. Half the calculated dose of bicarbonate (given below) should be added to the fluids and administered over 6 hours. If the acidosis is severe and acutely life threatening the dose may be administered slowly IV.

Dose Bicarbonate (mEq) =
Body weight (kg) x 0.4 x (12 – patient's bicarb)

It is important that correction of acidosis is done slowly, since overcompensation or rapid correction may cause metabolic alkalosis, paradoxical cerebral acidosis and a shift to the left of the oxygen dissociation curve, thereby limiting oxygen delivery. Cerebral acidosis results from rapid correction of plasma acidosis with the generation of carbon dioxide. Most of the CO_2 is removed by the lungs but some diffuses across the blood–brain barrier, recombines with water and generates hydrogen ions in the brain. Clinically these dogs will show progressively worsening of neurologic signs despite therapy.

Identify and Treat Precipitating Factors

If a source of infection is found, appropriate antibiotic therapy is indicated. In cases in which infection is suspected but not proven, antibiotics may be used empirically. Treatment of other concurrent disease states, such as pancreatitis and hyperadrenocorticism, must also be initiated as soon as possible so that DKA does not recur. In one study of ketoacidotic cats, ketoacidosis recurred in 42% of the cats that survived the initial episode. Testing for hyperadrenocorticism should be delayed until signs of DKA have resolved and patients are systemically well. If patients do not respond rapidly to treatment of DKA or have clinical signs that suggest additional diseases other than diabetes mellitus, an aggressive search should be made for other concurrent disease. Additional testing that may be indicated in individual patients includes thoracic radiographs to evaluate for congestive heart failure, neoplasia, pneumonia, and dirofilariasis; abdominal radiographs and ultrasound to identify pancreatitis, pyometra, or urolithiasis; and blood cultures if septicemia is suspected.

PROGNOSIS

In one large retrospective study of dogs with DKA, 70% of dogs survived to be discharged from the hospital, and median hospitalization was 6 days. Factors that negatively impacted survival included lower ionized calcium, lower hematocrit, lower venous blood gas, and larger base deficit.

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CUSHING'S AND OSTEOARTHRITIS: TREATMENT DECISION MAKING ILLUSTRATED

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Hyperadrenocorticism is common canine disorder associated with abnormally high circulating concentrations of glucocorticoids. In spontaneous hyperadrenocorticism, approximately 80% to 85% of cases are due to pituitary-dependent hyperadrenocorticism (PDH), with the remainder due to functional adrenocortical tumors (AT). A clinically identical syndrome may also be caused by the iatrogenic administration of corticosteroids. In this case the severity of clinical signs is directly related to the dose and duration of corticosteroid administration.

There are many profound metabolic consequences of hyperadrenocorticism that occur due to the effects of excessive circulating corticosteroids on gene transcription in the cell nucleus. Receptors for corticosteroids are present in almost all tissues. Once cortisol binds to cytoplasmic receptors, the hormone-receptor complex moves into the nucleus where it binds to DNA and has both stimulatory and inhibitory effects on multiple genes. These effects include increased protein catabolism, stimulation of lipolysis, increased hepatic gluconeogenesis, redistribution of body fat, insulin resistance, decreased gastrointestinal absorption of calcium, decreased bone density (osteopenia), inhibition of fibroblasts, multiple effects on leukocyte function and number, and inhibition of inflammation. Many of these effects directly or indirectly impact the neuromuscular system.

NEUROMUSCULAR DILEMMAS IN PATIENTS WITH HYPERADRENOCORTICISM

Exacerbation of Osteoarthritis Pain in Dogs Treated for Hyperadrenocorticism

Although many of the neuromuscular sequelae of hyperadrenocorticism resolve with effective treatment of hyperadrenocorticism, in some dogs orthopedic problems may not improve or may worsen with treatment. Because of the anti-inflammatory effects of glucocorticoids, osteoarthritis, which was not causing clinical signs prior to treatment, may start to become a clinical problem. In many cases, a good orthopedic examination prior to starting treatment will allow high risk dogs to be identified. Owners should be informed of the potential risk and a plan should be in place to deal with this problem if it should occur. Clinically, it appears there is a syndrome of severe osteoarthritis of multiple joints following treatment of hyperadrenocorticism. Such a syndrome has not been recognized in the literature, but may be as a result of high levels of steroids affecting both cartilage metabolism (adversely) as well as decreasing the stabilizing and protective function of muscles on joints. Regardless of the cause, it is imperative to:

- Perform a thorough orthopedic and musculoskeletal evaluation of patients prior to initiating treatment for hyperadrenocorticism
- Warn owners of the risk of worsening clinical signs associated with osteoarthritis, and that controlling the pain associated with this may be very difficult
- Not use nonsteroidal anti-inflammatory drugs (NSAIDs) to control OA pain until the endogenous production of steroid is under control. Use of NSAIDs increases the risk of gastrointestinal ulceration. When the hyperadrenocorticism is under control, periodic evaluation of this control is warranted if NSAIDs are used for pain control.

Options to treat pain associated with OA include:

- Treatment of hyperadrenocorticism and then treatment of OA pain with:
  - NSAIDs
  - Adjunctive drugs that may have an analgesic action (see Table 1)
  - Non-drug therapies that may have an analgsic action (see Table 2)
- Less stringent control of hyperadrenocorticism than would otherwise be ideal. Sometimes, after treatment of hyperadrenocorticism, the pain associated with OA is un-responsive to NSAIDs and adjunctive drugs, and less stringent control of hyperadrenocorticism can be used. In this scenario, NSAIDs are not used. If the dog was treated with surgery, then exogenous administration of steroids to control OA pain can be tried. In this case, NSAIDs should not be used.

Treatment of Joint Laxity as a Result of Hyperadrenocorticism

Hyperflexion of joints and joint laxity is a significant musculoskeletal problem associated with hyperadrenocorticism. Treatment of hyperadrenocorticism rarely improves any joint laxity present. The limitations of medical therapy to improve these manifestations of Cushing's need to be explained to the owner prior to stating treatment. The main points to remember about joint laxity are:

- Surgical intervention while the dog has high circulating levels of steroid is not advised
- Orthotics and braces can be used to help stabilize joints, but may exacerbate the laxity in the absence of therapeutic exercise

Management of Concurrent Orthopedic Problems in Dogs with Hyperadrenocorticism

Some patients with hyperadrenocorticism present with concurrent orthopedic problems that require surgical intervention (eg, rupture of the cranial cruciate ligament). In many cases it can be difficult to decide which problem to address first. In dogs with severe manifestations of Cushing's, the endocrine disease should be well controlled for 2 to 3 months prior to considering surgical intervention. Even then, surgical interventions for cranial cruciate ligament disease that do not rely on development of scar tissue (eg, TPLO, TTA) are preferred.

Dogs with severe Cushing's are poor surgical candidates for multiple reasons. These include predisposition to infection, poor respiratory function, delayed wound healing, cutaneous atrophy (complicates surgical recovery), and predisposition to thromboembolism. Any major surgical procedure should be delayed until good control of the hyperadrenocorticism is accomplished. Good clinical control of hyperadrenocorticism should result in normalization of the complications mentioned above and result in a much better surgical candidate.

Some dogs with hyperadrenocorticism are diagnosed based primarily on the laboratory abnormalities associated with Cushing's. These dogs may have minimal clinical signs of Cushing's disease at the time of diagnosis, and medical treatment is usually delayed until clinical signs develop. In this subset of dogs it is reasonable to consider surgical repair of neuromuscular problems if necessary without prior treatment of the Cushing's disease depending on the severity of the problem. If surgery is performed, consideration should be made for the likelihood of slightly delayed wound healing and other potential complications.

Conservative Management of Neuromuscular Problems in Dogs with Hyperadrenocorticism.

In dogs with hyperadrenocorticism, where treatment is not, for whatever reason, performed, conservative management of osteoarthritis and other neuromuscular problems is complicated by the risk of using non-steroidal anti-inflammatory drugs in a patient with high circulating glucocorticoid concentrations. Although the risk has not been well defined in the literature, it is there. NSAIDs should not be used in these patients. Instead, use should be made of adjunctive drugs that may provide analgesia, and non-drug therapies (Table 2) that may provide pain relief. If possible, body weight should be kept to a minimum.

Table 1. Adjunctive Drugs Used in the Management of Canine Osteoarthritis Pain

The following table outlines the doses for some of the oral drugs used by the author as 'adjunctive drugs' in the alleviation of chronic osteoarthritis pain in dogs. Although all the drugs are available in the United States, not all are approved for use in dogs. Many of the drugs have not had comprehensive efficacy, kinetic or toxicity studies carried out in the dog, and are being used empirically based on extrapolation from human medicine and the author's and colleagues clinical experience. There has been no comprehensive evaluation of the toxicity when these drugs are administered simultaneously. Evaluation of these drugs is being undertaken by a number of investigators and new information may result in changes in the recommended doses. These drugs are for use in combination with NSAIDs, steroids or acetaminophen; however, they can also be used on their own to provide pain relief in canine osteoarthritis. *In Cushingoid dogs, they may be used to provide some pain relief and they are compatible with excess endogenous or exogenous steroid.*

Drug	**Dose for Dogs**	**Comments**
Amantadine	4.0–5.0 mg/kg PO SID	• May take up to 2 weeks to see positive effects • Side effects appear to be mild agitation in some dogs • Marketed as 100-mg capsules. Suggest 1 capsule for dogs of 20–37 kg, and 2 capsules for dogs of 37–65 kg • Avoid use in congestive heart failure and seizure patients • Recent study suggests amantadine provides pain relief in addition to NSAID (not evaluated on its own)
Amitryptiline	0.5–2.0 mg/kg PO SID	• Bitter taste • Should not be used concurrently with tramadol
Gabapentin	5.0–10.0 mg/kg PO BID (can go up to 15 mg/kg TID)	• Side effects appear to be sedation
Polysulfated glycosaminoglycan (Adequan)	5 mg/kg IM twice weekly for 4 weeks, then once a month	• No noted side effects • Some evidence of efficacy in osteoarthritis pain.
Tramadol	4.0–5.0 mg/kg PO BID or TID	• Side effects appear to be sedation and vomiting (likely opioidergic effects) • Should not be used concurrently with amitryptiline

Table 2. Table of Non-Drug Treatments Useful in the Management of Painful Degenerative Joint Disease and/or Joint Laxity Associated with Cushing's Disease (Before or After Treatment of Cushing's)

Therapy	**Notes**
Decreased body weight	This can be difficult to achieve in dogs with Cushing's syndrome, but once the Cushing's is controlled/treated, weight management is of paramount importance. Weight reduction has been shown to increase limb use in canine OA, and reduced weight dramatically decreased the prevalence and severity of OA in dogs over their lifetimes.
Nutritional supplementation [glucosamine & chondroitin sulphate; ASU; omega-3-fatty acids]	There is now evidence from human studies that glucosamine & chondroitin sulfate combinations may provide some pain relief. The recently available Dasuquin, which has avocado/soybean unsaponifiables (ASU) added, may improved pain relief over glucosamine/chondroitin sulfate alone. There is some evidence of pain relief from ASU in humans with OA. Omega-3-fatty acids have also been shown to have pain alleviating properties when used as supplements.
Cold therapy	As yet, there is no evidence in canine medicine of a pain-relieving effect, but there is evidence of anti-inflammatory effects from basic science and human clinical studies
Heat therapy & Therapeutic ultrasound	Heating of muscles has been shown to increase the extensibility of muscle units, and decrease spasm
Stretching	Joint pain leads to muscle spasm, and stretching can release this spasm
Massage	Thought to be beneficial to patients with joint pain to alleviate muscle spasm associated with joint pain. Muscle spasm can be painful.
Electrical stimulation (TENS; NMES)	Transcutaneous electrical nerve stimulation; Neuromuscular electrical stimulation
Acupuncture	Whether acupuncture has pain relieving effects in canine osteoarthritis is debated, but clinically, dramatic effects can be seen.
Therapeutic exercise	Both active assisted and active exercise is considered to provide pain relief in painful degenerative joint disease in humans.
Ambulation assist devices	A variety of devices are available to assist with ambulation in canine patients with painful degenerative joint disease. Many are suitable in assisting Cushingoid patients, or patients with post-Cushingoid joint laxity, in ambulation (braces; orthotics, harnesses)
Optimizing the home environment	Many simple environmental modifications can be made to assist patients with painful degenerative joint disease and/or post-Cushingoid joint laxity to cope with their environment

DIFFERENTIATION OF FUNCTIONAL ADRENAL TUMORS FROM PITUITARY-DEPENDENT HYPERADRENOCORTICISM

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The adrenal gland is composed of two functional units, the cortex and the medulla. The cortex produces steroid hormones including glucocorticoids, mineralocorticoids, and androgens, while the medulla primarily secretes catecholamines. Functional tumors of both the cortex and medulla have been described in dogs and cats with the most common tumors being functional adrenocortical tumors. Approximately 15% to 20% of cases of hyperadrenocorticism (HAC) in both dogs and cats are due to the presence of an adrenocortical tumor (AT). Cortisol is the most common secretory product of adrenocortical tumors, but excessive production of other steroid hormones (sex hormones, mineralocorticoids) has been reported in both dogs and cats.

ADRENOCORTICAL TUMORS

Because most functional adrenocortical tumors secrete abnormal quantities of glucocorticoids, they cause clinical signs of Cushing's syndrome. Clinical signs include polydipsia, polyuria, polyphagia, abdominal enlargement, hepatomegaly, cutaneous changes (alopecia, cutaneous atrophy, calcinosis cutis, hyperpigmentation), muscle weakness, decreased exercise tolerance, excessive panting, truncal obesity, lethargy, weight gain, immunosuppression, insulin resistance, and decreased sexual function. Progestagens also have marked intrinsic glucocorticoid activity and therefore increased circulating concentrations of progesterone or 17- hydroxylprogesterone cause clinical signs that are indistinguishable from those due to glucocorticoids. Rarely, increased concentrations of adrenal androgens, estrogens, and mineralocorticoids, cause virilization, feminization, and hypertension, respectively.

Adrenocortical tumors are believed to arise spontaneously rather than due to chronic adrenocorticotropic hormone (ACTH) stimulation. Adrenocortical tumors are usually unilateral, and may be either adenomas or carcinomas. Excessive secretion of cortisol suppresses plasma ACTH concentrations by negative feedback on the pituitary and hypothalamus. The unaffected adrenal gland and normal cells in the affected adrenal gland are atrophic due to lack of stimulation by ACTH. Cortisol secretion from adrenocortical tumors is episodic. In most cases ACTH receptors are preserved and tumors respond to exogenous administration of ACTH. Cortisol secretion from adrenocortical tumors is unaffected by administration of exogenous dexamethasone.

Both right and left adrenal glands are affected with equal frequency. Approximately 50% of AT are adenomas, while 50% are carcinomas. Bilateral adrenal neoplasia may also occur. In some cases both tumors are adrenocortical in origin while in other cases one adrenal may contain an adrenocortical tumor while the second adrenal contains a pheochromocytoma. Concurrent pituitary and adrenal tumors have also been reported. Adrenocortical tumors occur most often in middle-aged to older animals. Females are at increased risk, as are dogs with a bodyweight greater than 20 kg. Canine breeds most commonly affected include poodles, German shepherds, dachshunds, Labrador retrievers, and terriers. No breed predisposition has been recognized in cats.

DIAGNOSIS OF ADRENOCORTICAL TUMORS

Diagnosis of Cushing's syndrome in both dogs and cats is made by consideration of historical findings, physical examination, review of laboratory minimum data base (CBC, serum biochemical profile, urinalysis) and performance of specific endocrine function tests (ACTH stimulation test, low-dose dexamethasone suppression test, urine cortisol:creatinine ratio). The ACTH stimulation test is less sensitive in diagnosis of AT than pituitary-dependent hyperadrenocorticism (PDH). Eighty-five percent of dogs with PDH have an abnormal ACTH stimulation test, whereas only 60% of dogs with AT have an abnormal ACTH stimulation test.

DIFFERENTIATION OF PDH FROM ADRENAL TUMORS

Clinical and routine laboratory findings are not useful in distinguishing PDH from functional adrenal tumors. The ACTH stimulation test and cortisol:creatinine ratio are also unable to differentiate adrenal tumors from PDH. Endogenous ACTH concentrations, and endocrine function tests such as the high- and low-dose dexamethasone suppression tests, are the most useful endocrine tests for distinguishing AT from PDH.

Low- and High-Dose Dexamethasone Suppression Tests

These tests are the most commonly used tests to differentiate pituitary dependent hyperadrenocorticism (PDH) from adrenal dependent hyperadrenocorticism (ADH). The tests rely on the assumption that adrenal tumors are more resistant to the feedback effects of dexamethasone than are hyperplastic or neoplastic pituitary glands. The protocol for the high-dose test (HDDS) is the same as the low-dose test (LDDS) except that the dose of dexamethasone is 10 times higher (0.1 mg/kg) and that a 4-hour sample is usually not collected. It is important that dexamethasone SP is used in this test because dexamethasone in polyethylene glycol can cause central nervous system signs at this high dose. Suppression is defined as a 4 or 8 hour plasma cortisol concentration that is < 50% of the baseline sample. One hundred percent of adrenal tumors will fail to suppress while 75% to 80% of pituitary-dependent cases will show suppression. Therefore, suppression after the low- or high-dose dexamethasone test is diagnostic for PDH. Lack of suppression, however, is not diagnostic for ADH and additional testing is required. If greater than 50%

suppression is seen at 4 or 8 hours on a LDDS, a HDDS test is unnecessary.

Endogenous ACTH Concentration

An understanding of the pathophysiology of HAC indicates that it should be possible to distinguish PDH from ADH based on the circulating ACTH concentration. In PDH, circulating plasma ACTH concentrations should be high while in ADH they should be low. Endogenous ACTH is susceptible to rapid enzymatic degradation in vitro so handling recommendations from the laboratory should be carefully followed. Different laboratories may have different reference ranges. In our laboratory ACTH concentrations >15 pg/mL are consistent with a diagnosis of PDH. ACTH concentrations <10 pg/mL are suggestive of ADH however some dogs with PDH will also have low values probably due to episodic ACTH secretion. The result of the endogenous ACTH should therefore never be relied on alone to confirm a diagnosis of adrenal tumor.

Additional tests that may be useful to differentiate PDH from ADH include abdominal radiography, abdominal ultrasound, and CT and MRI. Fifty to 60% of dogs with adrenal neoplasia have a radiographically visible mineralized mass on abdominal radiographs. In those AT in which mineralization is not evident, the neoplasm is usually identified by abdominal ultrasound. Computed tomography (CT) and or MRI may also be used to identify adrenal and pituitary masses. Results of the various differentiation tests can be difficult to interpret, particularly in the presence of bilateral adrenal neoplasia, concurrent AT and PDH, or concurrent pheochromocytoma.

In a recent study at Purdue it was shown that adrenocortical carcinomas secrete larger amounts of certain sex hormones in response to ACTH than do dogs with PDH, although there is large variability between dogs. Unfortunately this inter-dog variability means that this is not a useful clinical test for differentiating PDH from adrenal tumors (malignant or benign).

Staging of Adrenocortical Tumors

Because of the problems inherent in the histologic classification of endocrine tissues, it is often a diagnostic challenge for the pathologist to differentiate benign from malignant adrenal tumors, and to differentiate adrenocortical tumors from pheochromocytomas. It is therefore very important to consider biologic behavior of the tumor in addition to the histologic characteristics. History, physical examination, and laboratory testing (including endocrine function tests) are not useful in differentiating malignant from benign tumors; however, imaging studies may be useful. In general, large tumors (>50% of the size of the kidney) are likely to be malignant tumors, and evidence of vascular or capsular invasion, local extension, or metastasis are also predictive of malignancy. Adrenocortical carcinomas often invade local structures (kidney, liver, vena cava, aorta, retroperitoneum) and metastasize to the liver and lung.

SUMMARY

Differentiation of functional adrenal tumors from pituitary-dependent hyperadrenocorticism can be challenging. In some cases a variety of test need to interpreted together in order to localize the cause of hyperadrenocorticism. In most cases it is worthwhile to make this determination because the results may affect both treatment and prognosis.

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INDICATIONS FOR SEX HORMONE PROFILES IN DOGS

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Approximately 80% to 85% of cases of hyperadrenocorticism (HAC) in both dogs and cats are due to pituitary-dependent hyperadrenocorticism (PDH), with the remainder due to an adrenocortical tumor (AT). Cortisol is the most common secretory product of the adrenal gland in HAC, but excessive production of other steroid hormones (sex hormones, mineralocorticoids) has been reported in dogs and other species.

PHYSIOLOGY OF THE ADRENAL CORTEX

Adrenal steroids are derived from cholesterol and all contain the cyclopentanoperhydrophenanthrene (CPPP) nucleus. Four cytochrome P450 enzymes present in the adrenal cortex (17-alpha-hydroxylase, 3-beta-dehydrogenase, 21-beta-hydroxylase, and 11-beta-hydroxylase), catalyse formation of the different adrenal steroids. The adrenal cortex is composed of three layers, the zona glomerulosa (ZG), the zona fasciculata (ZF), and the zona reticularis (ZR). The ZG is the outermost layer of the adrenal gland and synthesizes and secretes aldosterone. The ZG is deficient in 17-alpha-hydroxylase activity, so it is incapable of synthesizing cortisol or androgens. The ZF and ZR both synthesize sex hormones and cortisol. Most sex hormones secreted from the adrenal gland are androgens (dehydroepiandrosterone, androstenedione).

Progesterone is synthesized in the adrenal gland as a precursor to androgens but in normal dogs very little progesterone is secreted into the circulation. Only small amounts of testosterone and estrogen are synthesized by the adrenal; however, adrenal androgens serve as substrates for synthesis of estrogen and testosterone in peripheral tissues. Cortisol production from the adrenal gland is regulated by corticotrophin-releasing hormone (CRH) released from the hypothalamus and ACTH from the pituitary gland. Regulation of adrenal androgen and estrogen secretion is poorly understood, but likely involves both ACTH and other non-ACTH pituitary factors.

CLINICAL SIGNS OF HYPERADRENOCORTICISM

In most cases of hyperadrenocorticism, secretion of abnormal quantities of glucocorticoids is believed to be the cause of the clinical syndrome (Cushing's syndrome). Clinical signs include polydipsia, polyuria, polyphagia, abdominal enlargement, hepatomegaly, cutaneous changes (alopecia, cutaneous atrophy, calcinosis cutis, hyperpigmentation), muscle weakness, decreased exercise tolerance, excessive panting, truncal obesity, lethargy, weight gain, immunosuppression, insulin resistance, and decreased sexual function. More recently it has been recognized that increased circulating concentrations of progesterone or 17-hydroxylprogesterone may cause clinical signs that are indistinguishable from those due to glucocorticoids. This is hypothesized to be due to the marked intrinsic glucocorticoid activity of progestagens. In rare cases of HAC, increased concentrations of adrenal androgens, estrogens, and mineralocorticoids may cause virilization, feminization, or hypertension, respectively.

DIAGNOSIS OF HYPERADRENOCORTICISM

Diagnosis of Cushing's syndrome is made by consideration of historical findings, physical examination, review of a laboratory minimum data base (complete blood count [CBC], serum biochemical profile, urinalysis) and performance of specific endocrine function tests (ACTH stimulation test, low dose dexamethasone suppression test, urine cortisol:creatinine ratio). Measurement of a baseline cortisol is of little value in evaluating the pituitary-adrenal axis in dogs with suspected HAC.

ACTH Stimulation Test

This is the most common test used in the diagnosis of HAC. It relies on the assumption that hyperplastic or neoplastic adrenals have abnormally large reserves of cortisol and that these animals therefore hyper-respond to maximal stimulation by ACTH. Most protocols recommend collection of a baseline sample, the administration of synthetic ACTH at a dose of 0.25 mg/dog IV or IM or 5 µg/kg IV. A second sample is collected one hour later. In order to interpret the ACTH stimulation test, normal values must be established for the individual laboratory. The ACTH stimulation test is abnormal in 85% to 90% of PDH cases and in 50% of ADH cases. The ACTH stimulation test does not distinguish between ADH and PDH. Because of the low sensitivity of this test, a diagnosis of HAC should not be excluded based on a normal ACTH stimulation. In situations in which sex hormones are measured, the same protocol for the ACTH stimulation test is used.

Low-dose Dexamethasone Suppression Test

This test is probably a better screening test for HAC since it is more sensitive (95%) than the ACTH stimulation test. It does not however, allow detection of iatrogenic Cushing's. This test relies on the fact that the administration of exogenous glucocorticoids should suppress the production of ACTH from the normal pituitary and therefore the production of cortisol from the normal adrenal. This suppression persists in the normal dog for 24 to 48 hours. Since dexamethasone is not detected by the assay for cortisol, this suppression can be measured after administration of exogenous dexamethasone. Adrenal tumors function independently of ACTH and a hyperplastic or neoplastic pituitary gland is relatively resistant to negative feedback from circulating steroids, so in either cause of hyperadrenocorticism no suppression after low dose dexamethasone administration occurs. The test requires a blood sample for the measurement of a baseline cortisol, followed by the administration of dexamethasone sodium phosphate IV at a dose of

0.01 mg/kg. The patient is then left undisturbed in a cage and a second blood sample is collected 8 hours later. In normal dogs the second sample will show suppression of the cortisol concentration to less than 1.5 µg/dL. Dogs with HAC will not suppress. Additional information may be obtained by measuring a 4-hour cortisol concentration. If suppression occurs at 4 hours but "escape" occurs at 8 hours this is diagnostic for PDH and further differentiation testing is unnecessary.

Urinary Cortisol:Creatinine Ratio

The urinary cortisol:creatinine ratio is a useful screening test for HAC. This test is performed on a voided morning urine sample so is a very convenient initial screening test. This test is extremely sensitive for HAC but is not very specific. Many other diseases other than HAC increase the cortisol:creatinine ratio. It is however useful in some circumstances in order to rule out HAC as a differential diagnosis. A dog with a normal cortisol:creatinine ratio is unlikely to have HAC.

Sex Hormone Panel

More recently evaluation of a sex hormones profile before and following administration of ACTH has been used to support a diagnosis of HAC. This is based on the finding that dogs with HAC also secrete excessive quantities of other adrenal steroids, in particular progesterone, 17-hydroxy-progesterone, androstenedione, and DHEA. Measurement of a sex hormone panel (University Tennessee Endocrinology Laboratory) before and after administration of ACTH may be useful in the diagnosis of early or atypical HAC. Sex hormone testing may also be useful in diagnosis of HAC caused by sex hormone secreting adrenal tumors (see later). In this case cortisol secretion is usually low normal or subnormal. Sex hormone profiles are expensive and the specificity and sensitivity for diagnosis of HAC are still being investigated. Therefore, it is important to know when the test is indicated and how to interpret the results.

ATYPICAL HYPERADRENOCORTICISM

This term has been used to describe cases of hyperadrenocorticism (usually PDH) in which clinical signs and response to treatment are consistent with a diagnosis of HAC, but the standard screening tests (ACTH stimulation test, low-dose dexamethasone suppression test) are normal. Note that in these cases, cortisol secretion is normal rather than suppressed as in the sex hormone-secreting adrenal tumors discussed in the next section. Initial studies suggested that sex hormone profiles might be a more sensitive screening test compared with cortisol alone for diagnosis of hyperadrenocorticism. More recent studies suggest that the sensitivity might not be as high as initially suspected; in fact recent studies in dogs with typical hyperadrenocorticism suggest that sensitivity of measurement of 17-hydroxyprogesterone specifically is lower than that of post-ACTH cortisol. Specificity of measurement of sex hormones in diagnosis of HAC is also not yet well documented. A recent study in a group of dogs with non-adrenal neoplasia that did not have hyperadrenocorticism suggested that specificity was as low as 70%.

NON-CORTISOL-SECRETING ADRENOCORTICAL TUMORS

In some adrenocortical tumors, cortisol concentrations are normal or suppressed rather than elevated and the tumor secretes excessive quantities of other adrenal steroids. Increased production of adrenal steroids other than cortisol may be due to deficiencies of one or more enzymes involved in normal steroidogenic pathways. Deficiency of these enzymes causes accumulation of precursor steroids proximal to the blocked step, with shunting of precursors into other metabolic pathways. Increases in enzyme activity can also play a role in steroid hypersecretion. In humans, adrenal carcinomas are often inefficient in conversion of cholesterol to cortisol and production of cortisol precursors is disproportionately high. In contrast adrenal adenomas exhibit very efficient steroidogenesis and production of precursors may be low or normal in relation to cortisol production. Whether this is also true in dogs is unknown; however, all reported cases to date of adrenal tumors in which the predominant secretory product is a steroid other than cortisol have been carcinomas.

In dogs with sex hormone secreting adrenocortical carcinomas, clinical signs are consistent with HAC, and adrenal tumors are identified by imaging studies, however endocrine function tests (ACTH stimulation, low dose dexamethasone suppression tests) do not demonstrate hypercortisolemia. Hormones that may be increased in different combinations included 17-hydroxyprogesterone, progesterone, estradiol, testosterone, and androstenedione. Surgical resection of sex hormone secreting tumors results in resolution of clinical signs and normalization of sex hormone profile abnormalities.

When Should I Run a Sex Hormone Profile?

At this time, it is not recommended that sex hormone screening is utilized for routine diagnosis of hyperadrenocorticism. This test should only be considered after routine adrenocortical testing has been completed. A sex hormone panel before and after ACTH stimulation should be considered in dogs that have clinical signs and clinical laboratory evidence of HAC, no evidence of other cause for their clinical signs, but normal or borderline cortisol testing (suspected atypical HAC). If the clinical signs do not support HAC (even if there are laboratory data that are suspicious) the sex hormone profile should not be recommended, because of the low specificity of the test. Sex hormone measurement should also be considered in dogs with clinical signs of HAC and suppressed cortisol concentrations after ACTH stimulation if treatment with exogenous steroids or mitotane can be ruled out (suspected sex hormone secreting adrenal tumors). Because the specificity of these profiles for diagnosis of HAC is still in question results should be interpreted cautiously. In dogs with suspected atypical HAC and appropriate clinical signs, abnormalities of at least two to three sex hormones (1.5 to 2.0 times the upper limit of the reference range) are consistent with a diagnosis of atypical HAC. In dogs with suspected sex-hormone secreting adrenal tumors, typically two to three hormones on the adrenal sex hormone panel are abnormal and concentrations are often extremely high. Cortisol concentration is typically low both before and after administration of ACTH. Definitive diagnosis of the presence of an adrenal tumor is best made by diagnostic imaging. The sex hormone profile is most useful in supporting the presence of an adrenocortical tumor rather than a pheochromocytoma. Consideration should also be given to the clinical presentation however, because some pheochromocytomas have been shown to have abnormal sex hormone concentrations after ACTH stimulation.

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DISORDERS OF CALCIUM REGULATION IN THE DOG AND CAT

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Hypercalcemia is a common endocrine abnormality seen in small animal practice. It occurs secondary to aberrations in calcium and phosphorus metabolism, most often secondary to neoplastic diseases or renal failure. Normally, calcium is absorbed from the intestinal tract via an active transport process. It is poorly absorbed and then 80% of the daily calcium intake is excreted in the feces and 20% is excreted in the urine. A constant source is therefore needed. Absorption is decreased by glucocorticoids and increased by vitamin D. Calcium is freely filtered at the glomerulus and reabsorbed from the tubules. Most is reabsorbed in the proximal tubule (70%) and ascending limb of Henle (20%). Renal control of reabsorption takes place at the distal tubule and collecting ducts and is under the control of parathyroid hormone (PTH). Most calcium in the body is stored in the bone with less than 1% being present in the serum. Of that which is in the serum about 50% is ionized (the active component) and the rest is chelated to organic anions or protein bound (mostly to albumin). As it is ionized calcium that is important clinically but total serum calcium that is usually measure it is important to recognize those factors that can influence serum and ionized calcium. Reduced albumin available for binding will result in a decrease in the total serum calcium proportional to the decrease in albumin. The ionized calcium will not be affected by a decrease in albumin but the total serum calcium will be reduced. The formula:

$$\text{Adjusted Ca (mg/dL)} = \text{Serum Ca (mg/dL)} - \text{Albumin (g/dL)} + 3.5$$

is used to adjust for any decrease in albumin and gives one an estimate of whether a low calcium is low solely because of a decrease in albumin or is low partially because of a likely decrease in ionized calcium as well. Changes in pH will cause shifts of Ca between protein bound/chelated and ionized. Therefore measured total serum calcium is not affected but relative concentrations of ionized calcium will be. Acidosis will increase the ionized calcium while alkalosis will decrease the ionized calcium. This can be important clinically when evaluating clinical signs and when considering treatment.

Ionized serum calcium is the most accurate measure of calcium having a pathophysiologic effect. Ionized serum calcium is under very fine control from Parathyroid hormone (PTH), Calcitonin, and Vitamin D. PTH is produced by chief cells in the parathyroid gland and released when ionized calcium is low. High-ionized calcium feeds back on the chief cells and inhibits PTH release. At bone, along with vitamin D, PTH increases the number and activity of osteoclasts, resulting in resorption of bone. This is the primary place where calcium is mobilized from in animals that become hypercalcemic. At the kidney PTH promotes activation of $25(OH)D_3$ to $1,25(OH)_2D_3$, promotes distal tubular reabsorption of calcium (also Mg, H^+, NH_4^+), and inhibits proximal tubular reabsorption of phosphorus (also K^+, HCO_3^+, Na^+, cAMP, amino acids). In the intestine, it is primarily vitamin D that is responsible for increasing Ca absorption. PTH is only indirectly involved. Calcitonin is produced in parafollicular (C) cells of the thyroid gland and released when serum ionized calcium is high. It decreases osteoclastic activity and blocks renal reabsorption of calcium. Vitamin D [$1,25(OH)_2D_3$ is the most active form] has its primary effects at the intestine (increase Ca absorption) and bone (promote resorption). It has minimal effect at the kidney.

CLINICAL SIGNS OF HYPERCALCEMIA

The clinical signs of hypercalcemia are fairly nondescript. They are best exemplified by those dogs diagnosed with primary hyperparathyroidism and include:

Dogs (based on 72 dogs with primary hyperparathyroidism; Feldman and Nelson, 1996):

PU/PD	70%
Anorexia	32%
Vomiting	12%
Listless	45%
Urinary signs	27%
Stiff gait	10%.
Weakness	40%
Shivering	17%
Constipation	10%

Cats (based on 45 cats with hypercalcemia of varying etiologies; Schenck, et al, 2006):

Urinary signs	47%
Anorexia	27%
Weakness	4%
Vomiting	31%
PU/PD	9%
Diarrhea	4%
Lethargy	31%
Weight loss	7%
Constipation	4%

Polyuria and polydipsia are the most often noted signs in dogs and can be quite dramatic. It is caused by inhibition of the effectiveness of ADH resulting in partial nephrogenic diabetes insipidus. Urinary tract signs including hematuria, dysuria, stranguria, pollakiuria, and inappropriate urination are noted most often in cats where the propensity of calcium crystal and stone formation is high in the hypercalcemic state. Other clinical signs are often seen in dogs and cats that are hypercalcemic but would be caused by the underlying disease that is resulting in the hypercalcemia.

DIFFERENTIAL DIAGNOSIS (FROM MOST TO LEAST COMMON)

One should initially be certain that the patient is indeed hypercalcemic as spurious hypercalcemia due to sample error, lipemia, or an unrepeatable result is a reason to see a high calcium on a chemistry panel. It is best to repeat the calcium determination before imparting on an expensive workup.

Hypercalcemia of Malignancy (Pseudohyperparathyroidism)

This is the most common cause of hypercalcemia in dogs. It is also a common cause in cats but idiopathic hypercalcemia and hypercalcemia associated with renal disease are also common in cats. Malignancy may result in hypercalcemia by many factors that increase bone resorption including; direct bony lysis by tumor produced cytokines, production of parathyroid hormone related protein (PTH-rP) or less commonly by production of PTH, activation of vitamin D or production of a vitamin D like substances. The most common tumor to result in hypercalcemia is lymphosarcoma (LSA) with about a third of dogs with LSA and less than 10% of cats with LSA being hypercalcemic. More than 90% have enlarged lymph nodes or mediastinal involvement. Few have no obvious tumor, however. Another important tumor to consider is anal sac apocrine gland adenocarcinoma. This is the most common perineal tumor of female dogs and 90% will be hypercalcemic. Multiple myeloma is another important cause of hypercalcemia. About 15% to 20% of dogs with multiple myeloma will be hypercalcemic. When it is seen, it is poor prognostic factor. Squamous cell carcinoma is a common reason for hypercalcemia in cats. Hypercalcemia associated with squamous cell carcinoma is seen at about the same prevalence as hypercalcemia associated with lymphosarcoma in cats. In general, animals with hypercalcemia of malignancy will have hypercalcemia but either hypophosphatemia or hyperphosphatemia may be seen.

Renal Failure

Hypercalcemia is seen in approximately 10% of dogs with renal failure. However, this is one of the most common causes of hypercalcemia in cats. It is more common in animals with congenital renal diseases (especially Lhasa apso, Shih Tzu, Doberman pinscher) but can occur in any breed, at any age. The mechanism can include autonomous parathyroid gland secretion (tertiary hyperparathyroidism), decreased renal calcium excretion, or increased responsiveness to vitamin D. Both hypercalcemia and hyperphosphatemia are generally seen.

Idiopathic Hypercalcemia in Cats

Idiopathic hypercalcemia is one of the most common causes of hypercalcemia in cats (along with hypercalcemia of malignancy and renal failure). The etiology is not currently known. All cats will have increased ionized calcium but as many as half will not show any clinical signs. There does not appear to be an age or sex predilection but longhaired cats are over represented. PTH concentrations are usually low or low normal and PTHrP is not usually detected. The role of diet has been debated but to date specific etiopathogenic factors have not been identified.

Primary Hyperparathyroidism

This is likely more common than is generally diagnosed because may animals will have mild increases in calcium and mild nondescript signs. The cause is usually parathyroid adenoma, which is often a small, non-palpable tumor of a single parathyroid gland. Parathyroid carcinoma is rare. Familial hyperparathyroidism is a rarely reported cause of primary hyperparathyroidism in young dogs. Diagnosis is usually made by demonstrating high or normal PTH concentrations in the face of high-ionized serum calcium. Parathyroid adenomas may be localized via ultrasound of the cervical region but the small size (usually less than 5 mm) makes this technique of low sensitivity except in the hands of very experienced ultrasonographers. Surgical exploratory of the cervical region and parathyroid biopsy is the means of definitively documenting this disease. Generally, hypercalcemia and hypophosphatemia will be noted.

Hypoadrenocorticism

Mild hypercalcemia is seen in about a third of dogs with hypoadrenocorticism. It is usually the dogs with more severe disease and most are also hyperphosphatemic. Hypoadrenocorticism is very rare in cats. Azotemia, hyperkalemia, hyponatremia, and hypoglycemia should cause one to consider hypoadrenocorticism. It is important to think of this very treatable cause of hypercalcemia because the clinical and laboratory presentation would otherwise be easily confused with renal failure.

Bone Disease

Hypercalcemia is uncommonly seen with diffuse osteomyelitis, primary or metastatic bone tumors, and disuse osteoporosis.

Granulomatous Diseases

Hypercalcemia has been reported with blastomycosis, histoplasmosis, coccidioidomycosis, pythiosis, and schistosomiasis. It is thought to be caused by mononuclear cell activation of vitamin D and cytokine release resulting in bone resorption. This is a rare cause of hypercalcemia unless one practices in an area where these infectious diseases are common. In Louisiana it is most commonly seen with blastomycosis, where as many as 10% of infected dogs may be hypercalcemic.

Hypervitaminosis D

Hypervitaminosis D may be due to excessive supplementation, ingestion of vitamin D rodenticides, or ingestion of vitamin D-containing plants. Hypercalcemia and hyperphosphatemia are seen. In animals in which excessive supplementation is the cause of hypercalcemia, the history is important. Large-breed pups are most commonly oversupplemented with vitamin D. Toxicity from vitamin D-containing plants (*Cestrum diurnum* [day-blooming Jessamine], Solanum malacoxylon, Trisetum flavescens) is uncommon in small animal medicine. Toxicity from vitamin D3 (cholecalciferol) rodenticides (Quintox®, Rampage®, Rat-Be-Gone®) is seen more commonly. Signs include hematemesis and bloody diarrhea, which separates cholecalciferol toxicity from other causes of hypercalcemia. Calcipotriene, a topical dermatological calcitriol analogue prescribed for the treatment of psoriasis in humans, has caused hypercalcemia from ingestion by licking the compound off of the owner's skin.

DIAGNOSTIC APPROACH

The following is list of diagnostic tests that may be part of an approach to the patient with hypercalcemia.

- **Repeat Serum Calcium** - An animal should not be considered hypercalcemic based on a single sample, especially if the sample is lipemic. Ionized calcium may help to differentiate hypercalcemia due to hyperparathyroidism and malignancy from hypercalcemia due to renal failure.
- **Go back to your Physical Examination** - Enlarged lymph nodes (rule out LSA), perianal mass (rule out apocrine gland adenocarcinoma of the anal sac)
- **Serum Chemistry Panel and Urinalysis**
  - Hypoalbuminemia - correct calcium.
  - Hypophosphatemia - prioritize hypercalcemia of malignancy or primary hyperparathyroidism.
  - Azotemia - prioritize renal failure. However, the question that comes up is whether the renal failure is causing the high calcium or is caused by it. Additionally, the azotemia can be difficult to catagorize into renal or prerenal causes because the high calcium itself will interfere with the ability to concentrate even if tubular function is still good.
  - Hyperkalemia - prioritize hypoadrenocorticism or renal failure.
  - Hypoglycemia - prioritize hypoadrenocorticism
- **CBC** - Helps rule out diseases that might cause inflammation
- **Thoracic and Abdominal Radiographs** – Rule out occult neoplasia, fungal disease. Radiographs of the thorax are especially important to rule out mediastinal lymphoma or fungal pneumonia.
- **Lymph Node Aspirate/Biopsy** – Rule out LSA
- **Bone Marrow** – Rule out LSA, multiple myeloma, and fungal disease.
- **PTH Concentrations** - Sshould be low when serum calcium is high. If high then prioritize primary hyperparathyroidism, renal failure, malignancy.
- **PTH-rP Concentrations** - Not done at very many labs but can be a marker of malignancy.
- Measuring serum concentrations of 1,25-dihydroxy-cholecalciferol can be helpful in ruling out vitamin D toxicity.
- **Ultrasound of the Neck** - May visualize parathyroid adenoma.
- **Steroid Trial** - Useful after infectious disease has been ruled out. The calcium will usually drop if the hypercalcemia is due LSA but not if it is due to other malignancy. This is an inconsistent test, however.

TREATMENT OF HYPERCALCEMIA

Hypercalcemia should be considered a medical Emergency if the calcium is greater than 18 mg/dL, the product of Ca x P is greater than 70 to 90, or if the animal is azotemia and/or dehydration is present. General principles of treatment include: 0.9% saline at a rate sufficient to replace deficits and twice maintenance. Saline infusion will increase GFR causing diuresis and calciuresis. Sodium rich solutions decrease tubular sodium reabsorption and thus calcium reabsorption is decreased. Furosemide (Lasix®) 2 to 4 mg/kg BID will inhibit reabsorption of calcium at the ascending limb. The animal must be rehydrated before diuresis will be effective. Glucocorticoids may result in tumor lysis (LSA) as a primary effect or may result in decreased GI calcium absorption, interfere with vitamin D activation, increase renal calcium excretion, and inhibit osteoclast activating factor. It should be noted, however, that steroids should initially be avoided until infection can be ruled out and tests for hypoadrenocorticism and LSA can be performed. Prednisone can be used at 1 to 2 mg/kg. Calcitonin (Calcimar®) can be used in an emergency to decrease of very high calcium concentrations. Bone resorption and renal reabsorption of calcium and phosphorus is inhibited. Bisphosphonates such as pamidronate disodium (1–2 mg/kg IV) also may be safe and effective in the treatment of hypercalcemia in dogs and cats. If the underlying disease process is known then specific therapy for that disease should be instituted.

HOW I MANAGE FELINE HYPERTHYROIDISM

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Feline hyperthyroidism is a multisystemic disorder caused by excessive production of thyroid hormones by abnormal thyroid tissue. It is most often caused by adenomatous hyperplasia of the thyroid gland. In 1% to 2% of cases the cause of thyrotoxicosis is thyroid carcinoma. Treatment options aimed at destroying or excising abnormal thyroid tissue include thyroid ablation via surgical thyroidectomy, radiation therapy via radioiodine, and chemical ablation via intrathyroidal ethanol injection. Cats undergoing thyroid ablation using iodine 131 have been shown to have significantly longer survival times when compared with cats treated with methimazole alone.[1] Surgical ablation, while generally safe and effective, is not without potential complications and recurrences.[2] While thyroid ablation is the ideal treatment, not all cats are immediately good candidates and not all owners choose to, or can afford such treatment. Medical treatment includes using antithyroid drugs of the thioureylene class, oral iodides, or reducing sympathetic tone with beta-adrenergic antagonists.

Methimazole is the antithyroid drug of choice in the medical treatment of feline hyperthyroidism. It is actively concentrated by the thyroid gland and acts as a general inhibitor of thyroid peroxidase-catalyzed reactions necessary for the formation of thyroid hormones and by binding to and altering thyroglobulin. Pharmacological studies in cats have shown that methimazole has good oral bioavailability. Serum half-life is 4 to 6 hours. Dosing recommendations are generally 5 mg orally 2 to 3 times a day. Specific dosing in individual cats is determined by dose titration to determine the optimal control of thyroid hormone production. This usually results in 2 to 3 times a day oral dosing. This can be difficult for some owners and is one of the reasons for poor owner compliance. Potential side effects that are dose dependent include anorexia, vomiting, and lethargy. Potential mild dose-dependent hematologic abnormalities include eosinophilia, leukopenia, and lymphocytosis. More severe hematologic abnormalities include agranulocytosis and thrombocytopenia while more severe clinical side effects include severe head pruritus and hepatic failure.

Because long-term oral administration of methimazole may limit owner compliance in some cases, use of a transdermal formulation of methimazole in a gel containing pluronic acid, isopropyl palmitate, and lecithin (PLO) has recently been offered by many custom compounding pharmacies that market to veterinarians. Initially, anecdotal evidence suggested that transdermal methimazole was effective but a pharmacokinetic study following a single transdermal dose of methimazole in healthy cats reported by Hoffman et al[3] found generally low to undetectable bioavailability relative to the oral route. Hoffmann et al[4] evaluated 13 hyperthyroid cats that were treated with transdermal methimazole at doses ranging from 2.5 mg once daily to 10 mg twice daily. The methimazole was formulated into a PLO-based vehicle (5 mg Tapazole per 0.1 mL) that was administered to the inner pinnae of the ear. While not all of the cats in the study became euthyroid there was a significant decrease in thyroid hormone when measured at both short-term (2.5 to 8 weeks) and long-term (3 to 7 months) follow-up. All cats showed clinical improvement. A larger controlled prospective clinical trial evaluating efficacy and safety of transdermal methimazole was reported by Sartor et al.[5] In this study 47 hyperthyroid cats were randomized into groups receiving either oral methimazole or transdermal methimazole. At 2 weeks a significantly higher percentage of cats receiving oral methimazole were euthyroid but this difference was no longer apparent by the 4-week recheck. There were fewer gastrointestinal side effects in the transdermal group implying that transdermal methimazole may be a safer alternative to oral methimazole, although the numbers of treated cats in each group with side effects were small. Head pruritus was not noted but anecdotal evidence has suggested that some cats with head pruritus while on oral methimazole may not show facial and head excoriations if switched to a transdermal formulation. Head pruritus has been reported with transdermal administration of methimazole.

In conclusion, transdermal methimazole does not appear to have as good a bioavailability as oral methimazole but has proven effective in controlled studies of efficacy and safety. The power of studies reported are low but side effects appear to be less common and owner compliance appears to be better when compared with the oral route of administration. Further study is required before definitive clinical recommendation can be made but transdermal administration appears to be a viable option for owners who have difficulty giving oral medications.

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ARTHROSCOPY FOR THE SMALL ANIMAL PRACTITIONER

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Major advancements in diagnosis and treatment have been made in veterinary arthroscopy during the past 15 years, and its use has become common for joint diseases in dogs. The goal of this article is to review the most common uses of the technique in the different joints.

HISTORY OF VETERINARY ARTHROSCOPY

The first use of arthroscopy in veterinary surgery occurred in horses in Europe, and by the mid-1980s, arthroscopy in equine surgery was becoming commonplace. Today, arthroscopy for the diagnosis and treatment of equine orthopedic diseases is well accepted and routine.

The development of arthroscopy in small animal surgery has lagged behind that of the human and equine fields because of the lack of small joint instrumentation, cost of equipment, and skepticism regarding its practicality and efficacy. The initial description of the use of an arthroscope in dogs was done by Siemering, who reported findings of stifle arthroscopies and concluded that the instrumentation was useful in the diagnosis of diseases of the canine stifle joint. At about the same time, Bennett and Kivumbi from the United Kingdom reported the usefulness of arthroscopy for the canine stifle joint. Techniques in small animal arthroscopy were substantially advanced by the work of Person, who reported techniques for arthroscopy of the canine stifle, shoulder, and coxofemoral joint and described the first successful use of arthroscopy in the treatment of osteochondritis dissecans of the shoulder. Since that time, the field of small animal arthroscopy has developed through publication of advanced techniques in Europe and the United States, the development of instrumentation specifically designed for small animal arthroscopy, and the establishment of instructional courses worldwide.

ADVANTAGES, DISADVANTAGES, AND COMPLICATIONS OF ARTHROSCOPY

The advantages and the disadvantages are summarized in Table 1. Arthroscopy is a minimally invasive technique, which permits a thoughtful and detailed inspection of all major joints in dogs.

The considerable magnification and mobility of the instruments within the joint permit accurate observation of intra-articular structures and their pathologic changes. Arthroscopy can reveal discrete or early articular lesions when radiography fails to demonstrate evidence of disease.

There is little morbidity and minimal risk of complications. The two greatest disadvantages of small animal arthroscopy are the cost and care of the equipment and the training and experience required for practical application. In summary, arthroscopy results in less surgical morbidity, less postoperative pain, and faster recovery compared with arthrotomy, and multiple joints can be treated the same day.

INSTRUMENTATION

Understanding and selection of arthroscopy equipment are vital to the success of arthroscopy. Of primary importance is the quality of the optical system.

Table 1. Pros and Cons of Arthroscopy

Advantages:

- Decreased patient morbidity (decreased hospitalization and postoperative costs)
- Simultaneous treatment of several joints
- Minimal invasiveness (reduced postoperative pain and soft tissue damage)
- Quick patient recovery and return to function
- Less scarring
- Periodic reevaluation of the joint is possible
- Improved visualization of intraarticular surfaces and structures
- Reduced surgical risk of infections and complications
- Video connection allows visualization and is useful for teaching

Disadvantages:

- The equipment is expensive and fragile
- Training is required
- The arthroscope and instruments are difficult to manipulate in small joint spaces
- **Complications:**
    - Extravasation of fluid in the surrounding soft tissues
    - Iatrogenic damage to the articular cartilage
    - Obstruction of view by hemorrage, hyperplastic villi, or the fat pad
    - Neurologic injury

The equipment must be able to provide an excellent image to enable precise inspection, diagnosis, and therapy. The quality of observation is supported by appropriate fluid control. The establishment and maintenance of adequate fluid flow during the procedure is necessary order to maintain observation. This depends on the ingress and egress (inflow and outflow) system and the gravity or fluid pump system.

Finally, successful biopsy or therapy requires small, high-quality hand instruments. Proper selection and care of the appropriate equipment enable years of reliable service. The modern arthroscope consists of a telescope and eye piece. The telescope contains a series of fiberoptic cables that carry light into the joint and a tubular lens that carries the image back to the eyepiece. Arthroscopes are differentiated by diameter (1.0, 2.4, 2.7 mm and larger), length (short, long), and angle in degrees (0°, 30°, 70°). Arthroscopes in common use in small animal arthroscopy include any of the diameters and lengths listed; most have a 30° angle. The diameter applies to the telescope portion alone and does not include the diameter of the arthroscope cannula that is necessary for use. The selection of diameter is based on the size of the joint and the surgeon's preference; larger scopes provide more rigidity and greater field of view, and smaller scopes cause less trauma and have greater mobility.

Whereas it is possible to perform arthroscopy directly through the eyepiece of the arthroscope, it is generally impractical. The image of the arthroscope is conveyed to a television monitor through a digital camera that is attached to the eyepiece. Cameras are available with one or three chips and must be used with a specific camera box that processes the image for the television screen. For general use, one-chip cameras provide excellent resolution and recording capabilities, and three-chip cameras are generally necessary only for higher-end video or still image work. Medical-grade monitors are recommended to provide a bright, clear, and accurate image.

Lighting within the joint is provided by a light source and is directed to the joint by a light cable attached to the fiberoptics within the arthroscope.

Hand instruments include probes, knives, curettes, and forceps. The most commonly used probes are right angled. Numerous styles of knives and curettes are available for manipulation of soft tissue.

The most common forceps used in small animal arthroscopy are graspers for removal of hard or soft tissues and biters, baskets, and punches for debridement of soft tissues.

INDICATIONS FOR ARTHROSCOPY

Nowadays, any major joint can be explored and multiple diseases are treated under arthroscopy by the expert veterinary arthroscopist. A list of the most common indications may be found in Tables 2 and 3.

Table 2. Diagnostic and Surgical Applications of Arthroscopy in the Forelimb of Dogs

Shoulder:
- Osteochondritis dissecans (OCD)
- Diagnostic examination (eg, biopsy of bone, cartilage, or synovial membrane)
- Shoulder instability (eg, joint capsule or ligament tears)
- Incomplete fusion of the caudal glenoid ossification center
- Cartilage fracture
- Reduction and stabilization of a supraglenoid tuberosity avulsion
- Intra-articular fractures
- Bicipital tenosynovitis
- Septic arthritis

Elbow:
- Osteochondritis dissecans (OCD)
- Fractured medial coronoid process (FMCP)
- Ununited anconeal process (UAP)
- Treatment of severe degenerative joint disease associated with elbow dysplasia
- Fractures of the humeral condyle, with closed reduction and fixation
- Diagnostic examination (biopsy of bone, cartilage, or synovial membrane)
- Septic arthritis

Carpus:
- Evaluation of ligamentous damage
- Intra-articular fractures and removal of small bone chips
- Carpus instability
- Diagnostic examination (biopsy of bone, cartilage, or synovial membrane)
- Septic arthritis

Table 3. Diagnostic and Surgical Applications of Arthroscopy in the Hindlimbs of Dogs

Hip:
- Hip dysplasia (pre and postoperative evolution of TPO)
- Osteoarthritis
- Hip dislocation
- Post-traumatic hip pain
- Diagnostic examination (eg, biopsy of bone, cartilage, or synovial membrane)
- Septic arthritis

Stifle:
- OCD lesions of the lateral and medial femoral condyle
- Injuries of the cranial cruciate ligament: preoperative cruciate ligament evaluation, cruciate repair failure evaluation
- Injury of the caudal cruciate ligament
- Meniscal examination and treatment (eg, meniscectomy, meniscal release)
- Long digital extensor or popliteal ligament avulsions
- Repair and debridement of avulsion fractures of the cranial cruciate ligament and caudal cruciate ligament
- Foreign body
- Osteoarthritis
- Acute trauma of the stifle
- Acute traumatic medial patellar luxation and grade 1 and 2 patellar luxation
- Diagnostic examination (eg, biopsy of bone, cartilage, or synovial membrane)
- Septic arthritis

Tarsus:
- OCD
- Malleolar and intra-articular fractures
- Osteoarthritis
- Joint instability
- Diagnostic examination (eg, biopsy of bone, cartilage, or synovial membrane)
- Septic arthritis

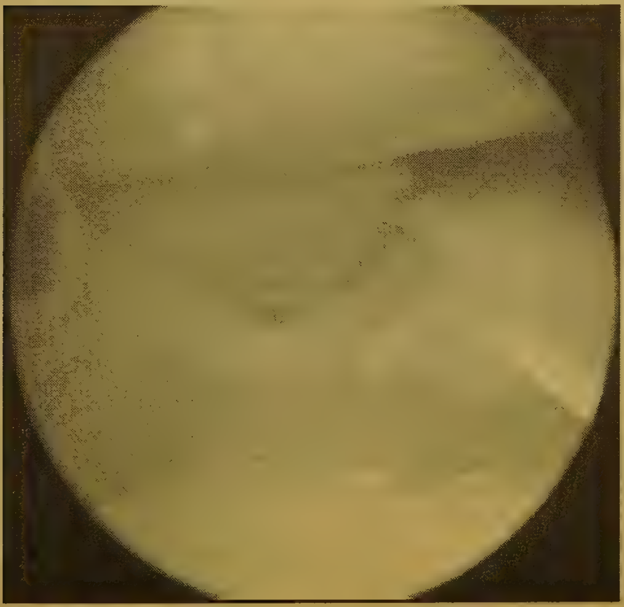

Figure 1. Medial view of a right elbow with FCP associated with a medial compartment syndrome.

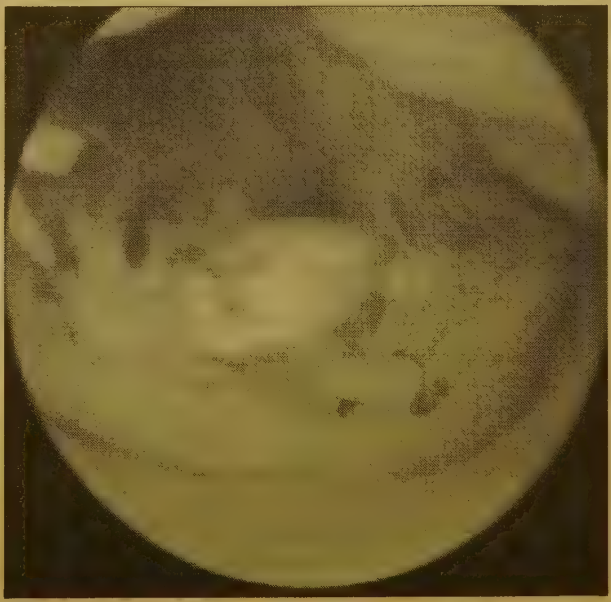

Figure 2. Arthroscopic view of a tear of the insertion of the biceps tendon.

The most common indications for arthroscopy in dogs are the diagnosis and treatment of FCP and OCD of the elbow, treatment of shoulder OCD and diagnosis and treatment of shoulder joint instability, pre- and postoperative evaluation of cranial cruciate rupture, pre- and postoperative evaluation of the hip joint-associated triple pelvic osteotomy (TPO), tarsal and stifle OCD, and exploration of any suspected painful joint.

CONCLUSIONS

Arthroscopy appears to be as important a breakthrough for the veterinary orthopedist as radiology and the CT scan have been for radiologists. Nowdays the diagnosis of articular diseases has been refined, particularly for diseases of the shoulder joint, and many surgical procedures are done using minimally invasive arthroscopy. Arthroscopy results in less surgical morbidity, less postoperative pain, and faster recovery. Multiple joints maybe treated the same day. The future of arthroscopy is bright in small animal surgery: more veterinarians will be able to practice, more articular diseases will be treated under arthroscopy, and smaller joints will be explored arthroscopically.

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THORACOSCOPY IN SMALL ANIMAL SURGERY

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PERICARDIAL WINDOW

Creation of a window in the pericardium establishes permanent drainage for patients with pericardial effusion. This technique is performed effectively with minimally invasive technique with greatly reduced operative trauma and postoperative pain. Indications for permanent pericardial drainage include neoplastic effusions, hemorrhage from neoplastic masses, inflammatory disease, and idiopathic effusions. This procedure prevents cardiac tamponade in the future by allowing drainage of pericardial fluid in the pleural space. Results with this procedure are excellent with long-term resolution in cases with idiopathic or inflammatory disease and dramatically improve quality of remaining life in cases with neoplasia.

Approach

To perform a pericardial window the patient is placed in dorsal recumbency and a para-xiphoid telescope portal is established. There are two options for placing operative portals. The first places both portals on the right side and the second places one portal on the right side and one on the left side. Each has advantages and disadvantages with the choice between the two related mostly to surgeons preference. The first option places operative portals in the right 6th or 7th intercostal space and in the right 9th or 10th intercostal space. The second option places portals in the left and right 9th to 10th intercostal spaces. All portals are placed ventral to the costochondral junction in the area of the lateral margin of the transverse thoracic muscles. As an alternative, an intercostals approach can also be performed. The patient is placed in left lateral recumbency, and the camera portal is placed in the ventral third 6th or 7th intercostal space. Two instrument portals are then placed in the 4th intercostal and the 8th intercostal spaces. This approach allows a better visualization of the right atrial appendage and aortic root for heart base tumor. A pericardial window will then performed on the right side of the pericardium. The phrenic nerve has to be identified prior to incising the pericardium.

Surgical Technique

The surgeon stands on the right side of the patient for the first technique and on either side of the patient for the second technique. The telescope operator stands at the foot of the patient or across the patient from the surgeon. Obliquing the patient slightly to the left (10 to 15 degrees) can facilitate visualization and manipulation when both portals are placed on the right side. With all portals in place the first step of the procedure is to cut the ventral mediastinum off of the sternum to get it out of the visual and manipulative field. Scissors are used to cut the mediastinum with electro surgical assistance for control of bleeding. Inadequate control of bleeding from the mediastinal vessels interferes with the procedure by allowing blood to drip onto the telescope and obscure visualization. It is recommended to explore the cranial mediastinum for lymph node enlargement and biopsy. Biopsy of the lymph node may reveal the diagnosis of mesothelioma of the pericardial that might not diagnosed on the pericardial window sent for histology.

A site is selected for the pericardial window on the cranial surface of the heart. When the pneumothorax is established with the patient in dorsal recumbency the apex of the heart falls dorsally presenting the cranial surface of the heart to the surgeon rather than the apex that would be seen without the pneumothorax present. Babcock forceps or aggressive grasping forceps with teeth are used to pick up a fold of pericardium and Metzenbaum scissors are used to cut into this elevated fold of tissue for initial penetration of the pericardium. This technique minimizes the potential for cardiac damage. The graspers are repositioned to pick up a margin of the initial pericardial incision. Any excess pericardial fluid that has not been previously evacuated and that interferes with visualization is removed with suction. The pericardial incision is extended to remove a patch of pericardium taking care not to damage the phrenic nerves, heart, lungs, or great vessels. There is no scientific data to define how much pericardium to remove. The portion removed needs to be large enough to prevent closure of the defect by the healing process and small enough to preclude herniation of the heart through the window. A one-inch square patch has been an acceptable size. The removed patch is extracted from the chest through one of the operative portals and is inspected for size and to define pathology. Samples are submitted for histopathology and if indicated for cultures.

Any residual pericardial and pleural fluid is removed with suction and the cavities are irrigated with saline. Operative portal cannulas are removed and the portals closed in layers to achieve an airtight closure. A thoracostomy drain is placed as a routine fashion through the chest wall. Placement of the tube can be controlled with the thoracoscope.

SUBTOTAL PERICARDIECTOMY

The primary indication for subtotal pericardiectomy is constrictive pericarditis. Subtotal pericardiectomy may also be indicated for infectious processes or neoplasia involving an extensive area of the pericardium. The dissection for subtotal pericardiectomy is much more difficult than for creating a pericardial window and is therefore not indicated for management of pericardial effusion. Patient positioning and portal placement are the same as for the pericardial window procedure but two portals may be required on each side of the chest for completion of dissection. Phrenic nerves are identified. Pericardium will be incised ventral to the phrenic nerve. Phrenic nerve could be elevated off of the pericardium to allow resection of more pericardium than can be accomplished if the incision is kept ventral to the nerves. Pericardial excision is started with the same technique as for creating a pericardial window but the pericardial incision is extended as far cranially and dorsally as possible and then circumferentially in each direction from the cranial end of the initial incision. Electrosurgical assistance is used as needed for hemostasis. Portal closure, chest tube placement, and postoperative management are the same as for a pericardial window.

PARTIAL LUNG LOBECTOMY

Lung biopsy for chronic lung disease, excision of lung masses, lung abscesses, emphysematous bullae, or any other localized disease process in the peripheral portions of the lung lobes can be performed quickly and effectively with minimally invasive technique. Partial lung lobectomy can also be performed for diagnostic biopsy of generalized lung disease.

Approach

Portal placement for partial lung lobectomy is dictated by the location of the lung to be removed. Dorsal recumbency and the para-xiphoid telescope portal allows examination of both sides of the chest for cases where the side of the pathology cannot be determined such as with spontaneous pneumothorax. If the side of involvement can be determined preoperatively with radiographs or other diagnostic techniques lateral recumbency provides greater unilateral access and is the preferred position. The telescope and operative portals are inserted using appropriate triangulation to access the involved pathology.

Surgical Technique

For small peripheral lesions and for lung biopsies a loop ligature technique can be used. The tip of the lobe to be removed is positioned through a pretied loop ligature (Endoloop) which is tightened and the ligated portion of the lung is transected and removed. This technique is quick, easy, and saves the significant expense of an endoscopic stapler. Larger or more central lesions require an endoscopic stapling device (Endo GIA) for occlusion and transection of the portion of the lobe to be removed. When performing partial lung lobectomy with an endoscopic stapler the telescope and operative portals are placed, the lung lobe lesion is defined and retracted or elevated as needed, and the endoscopic stapler is placed through an additional portal to provide optimal alignment for application of the stapler. Because of the cost of endoscopic staple cartridges the longest staple cartridges (65 mm) are used to minimize the chance of needing to fire two cartridges. Following transection of the lung lobe the excised portion is removed from the chest by enlarging one of the portals to allow passage of the tissue. An endoscopic tissue pouch (Endopouch) can be used to facilitate tissue removal. The transected lung margin is observed for air leakage or bleeding prior to exiting the chest with the telescope. A chest drain is placed at a site away from all portals, operative and telescope cannulas are removed, and the portals are closed.

LUNG LOBECTOMY

Complete lung lobectomy can also be performed with minimally invasive technique. Lung lobes with small masses and away from the hilus of the lung can be removed with minimally invasive surgery. Large masses impair visualization of the hilus of the lung and make manipulation of the lung difficult.

Approach

Lateral recumbency with intercostal portal placement is the preferred technique for complete lung lobectomy. One lung ventilation is recommended to increase the amount of space available in the thoracic cavity to manipulate the instruments and the lung mass. A telescope portal and two operative portals are placed with triangulation and the hilus of the lung lobe to be removed is prepared with sharp dissection.

Surgical Technique

For caudal lung lobes the pulmonary ligament is divided to free the lung lobe for manipulation into position for placement of the endoscopic stapling device. Individual structures of the hilus are not isolated for minimally invasive lung lobectomy and are separated from surrounding structures only enough to place the stapling device. A 45-mm to 65-mm-long stapling cartridge with 3.5-mm staples is placed across the hilus of the lobe to be removed through its own additional portal that is placed ventrally and caudally at a location to allow the stapler to be placed perpendicular to the bronchus and blood vessels. The stapling cartridge must be long enough to include the entire hilus to be stapled. The resected lung lobe is removed from the chest through a small intercostal thoracotomy. Enlarged hilar lymph nodes can be biopsied or removed with minimally invasive technique. If a lymph node is to be dissected and removed for biopsy sharp and blunt dissection are used for lymph node removal with electrosurgical assistance and clip application for hemostasis. An endoscopic tissue retrieval pouch facilitates removal of the lung lobe and decreases the potential of seeding neoplastic cells or infection to the chest wall. Prior to removal of the telescope the hilus is observed for air leakage or bleeding. A chest drain is placed at a site away from all portals, the operative and telescope cannulas are removed, and the portals are closed.

PERSISTANT RIGHT AORTIC ARCH CORRECTION

Minimally invasive transection of the ligamentum arteriosum in cases with persistent right aortic arch (PRAA) has been shown to be an effective alternative to the open surgical approach.

Approach

To perform minimally invasive PRAA correction the patient is placed in right lateral recumbency, the telescope portal is placed in the left 4th or 5th intercostal space at the costochondral junction, and operative portals are placed in the 3rd and 6th or 7th intercostal space at the level of the costochondral junction and at the dorsal end of the 5th intercostal space.

Surgical Technique

A retractor is placed in the 6th or 7th intercostal portal to retract the cranial lung lobe caudally. A stomach tube is placed in the esophagus to improve visualization of the ligamentum arterisosum. A palpation probe is used to further localize the ligamentum arteriosum. The ligamentum arteriosum is dissected with sharp and blunt dissection to isolate it from the pleura and esophagus. Identification of the esophagus during dissection is facilitated by passing a stomach tube or an endoscope. Endoscopic 5 mm vascular clips are placed on the isolated ligamentum arteriosum and it is transected between the clips. Any remaining fibers are dissected off of the esophagus and divided and the esophagus is dilated by passage of a balloon dilation catheter or esophageal bougies. A chest tube is placed and the portals are closed. Postoperative dietary management is the same as for open surgical PRAA correction.

MEDIASTINAL AND PLEURAL MASS EXCISION

Selected neoplastic, (thymoma) and inflammatory masses can be removed effectively with minimally invasive technique. Masses that are inoperable with minimally invasive technique can be evaluated for open surgical resectability or biopsied and staged for appropriate non surgical treatment. Patient position and portal placement is defined by location of the mass. Cranial mediastinal masses are visualized most effectively in dorsal recumbency with a para-xiphoid telescope portal. Operative portals can be placed with both portals on one side of with bilateral portals. Intercostal space selection for the operative portals again depends on the location and size of the cranial mediastinal mass. Portals are placed as ventrally in the appropriate intercostal spaces as possible without traumatizing the internal thoracic artery. Masses are dissected with sharp and blunt dissection as indicated with ligatures, vascular clip, and electrosurgical assistance for hemostasis.

Patient position and portal placement for approach to pleural masses in locations other than the cranial mediastinum are strictly dependent on the location of the mass.

Other procedures that have been performed under thoracoscopy are PDA ligation, and thoracic duct ligation.

The most important benefit from thoracoscopy in small animal surgery is the fast recovery. Since there is no rib retraction during thoracoscopy and limited incision even to exteriorize a mass, the amount of pain postoperatively is significantly reduced when compared with thoracotomy. There are no objective data in veterinary literature to demonstrate the advantage of thoracoscopy.

INTRODUCTION TO FLEXIBLE GI ENDOSCOPY

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Endoscopy is now a well established procedure in veterinary medicine. An endoscope is one of the most versatile and diagnostically valuable pieces of equipment that a veterinary practice can have in its armamentarium. The purpose of this article is to familiarize veterinarians with the principles of flexible fiberoptic instrumentation and to review indications for use of endoscopy in patients with gastrointestinal disorders.

INSTRUMENTATION

Flexible endoscopes have channels for water flushing, air insufflation, and suction. These capabilities greatly improve the endoscopist's ability to perform a thorough examination. Air is supplied by a pump within the light source and is emitted from a nozzle in the distal tip. Air is used to distend the walls of the organ being examined so that they do not obstruct examination by collapsing around the tip of the endoscope. Water is forced through a pressurized container and serves to flush mucus and other debris away from the tip of the endoscope. Fluid and air can be suctioned through the working channel of the endoscope into a suction unit attached to a port on a section of the light source connector.

Most flexible endoscopes have two-stage flexibility, with the most distal portion (approximately 6 cm) being more flexible than the proximal portion. Depending on the endoscope, the distal tip can be deflected using knobs on the control housing in either two or four directions. Tip deflection enhances maneuverability as the endoscope is advanced through the various curves and angles of the GI tract. Four-direction deflection capability allows for endoscope tip excursion through a variety of planes. The endoscopist then has the opportunity to perform a more thorough examination and to obtain samples from any mucosal area within reach. Four-direction capability is strongly preferred over two-direction for gastrointestinal endoscopy.

An instrument channel housed in the endoscope is used to pass biopsy forceps, cytology brushes, foreign body graspers, and other ancillary instruments. The same channel is used for suction. Depending on the size of the endoscope, the working channel diameter generally varies from 2.0 to 2.8 mm in GI endoscopes. Biopsy instruments small enough to pass through a 2-mm working channel can be used to procure excellent biopsy samples. Instruments are advanced through the working channel port, which is located near the control section.

In addition to the endoscope and light source, a suction pump, biopsy forceps, foreign body grasper, and brushes for obtaining cytology samples should be available. The ancillary instrument used most often for gastrointestinal endoscopic examinations is the biopsy forceps. The most common reason for performing gastrointestinal endoscopy is to both examine **and** obtain biopsies from the areas being examined, regardless of gross appearance. Examination without biopsy may result in inaccurate diagnosis.

SELECTION OF AN ENDOSCOPE

My recommendation to veterinarians interested in purchasing their first endoscope is to purchase a single high-quality endoscope that may be used for a variety of procedures (eg, esophagogastroduodenoscopy, colonoscopy, bronchoscopy, reproductive endoscopy) in small cats and dogs as well as in large dogs. A pediatric endoscope with four-way tip deflection capability meets these criteria. The insertion tube diameter should range from 7.8 mm to 9.0 mm. The major limitation of a large insertion tube (greater than 9.0 mm) is that there is more difficulty in passing it through the pyloric canal to the duodenum in cats and small dogs. The larger 9.0- to 9.8-mm endoscopes can be used quite effectively in many animal patients, but there are inherent difficulties in performing a complete examination in very small patients. This becomes an important consideration for any urban practice in which many feline and small canine patients are seen. A standard working length of 100 cm or more is adequate for performing a thorough examination in dogs and cats. Newer veterinary pediatric endoscopes are available in a diameter of 8.5 mm and a length of 150 cm (Storz) and 7.9 mm/140 cm (Olympus). These long and narrow diameter endoscopes can be used in cats as well as in giant breed dogs. An advantage of these longer endoscopes is that they always provide sufficient length to reach the duodenum in even the largest of dogs. In some larger dogs a 100-cm-long scope is insufficient for reaching and entering the duodenum.

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ESOPHAGOSCOPY AND GASTROSCOPY

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ESOPHAGOSCOPY

The term *esophagoscopy* refers to examination of the lumen and mucosal lining of the esophagus with endoscopic equipment. Esophagoscopy is indicated for the evaluation of animals with signs of esophageal disease, including regurgitation, dysphagia, odynophagia, and excessive salivation. This noninvasive modality allows visual examination of the esophageal mucosa and lumen and facilitates the procurement of specimens for biopsy, cytology, and culture. Thus, esophagoscopy is most effective for obtaining a definitive diagnosis of conditions involving the mucosa or abnormalities within the lumen, including esophageal foreign body, esophagitis, esophageal stricture, esophageal neoplasia, diverticulum, vascular ring anomaly, and gastroesophageal intussusception. Compared with contrast radiography, esophagoscopy is less definitive for diagnosing megaesophagus and other motility disorders, diverticulum, hiatal hernia, and compression by peri-esophageal masses, although it often provides valuable diagnostic information in these situations. Esophagoscopy can also be used as a therapeutic intervention to dilate esophageal strictures, remove esophageal foreign bodies, place indwelling gastrostomy or esophagostomy feeding tubes, and ablate neoplastic tissue with lasers.

Procedure

The anesthetized and intubated patient is placed in a left lateral recumbent position with an oral speculum securely in place. The endotracheal tube is particularly important for preventing the aspiration of refluxed or regurgitated material from the oropharynx during the procedure.

With the animal's head and neck extended, the endoscope is directed centrally through the oropharynx and guided dorsal to the endotracheal tube and larynx so that the cranial esophageal sphincter (CES) comes into view. The CES is the entrance to the esophagus and is normally closed, appearing as a star-shaped area of folded mucosa dorsal to the larynx. With insufflation and minimal pressure of the endoscope tip against the CES, the scope is easily advanced through the low-resistance sphincter into the cervical esophagus.

The cervical esophagus is normally collapsed so that as the endoscope passes through the sphincter, a brief "redout" usually obscures visibility. Thus before the scope is advanced farther, the esophagus should be insufflated with air until the lumen is clearly visualized. Within the esophagus, the endoscope should meet little or no resistance as it is advanced. The esophagus is essentially a straight tube except for a light flexure at the thoracic inlet, where the cervical and thoracic esophagus meet. The operator should advance the scope down the esophagus in a slow continuous motion, using only minor adjustments in tip deflection and torque to maintain a full panoramic view of the lumen and mucosal surfaces. Air should be insufflated intermittently to keep the lumen open. The lumen of the thoracic esophagus generally opens with minimal insufflation. Pulsations of the aorta are seen at the level of the base of the heart.

Appearance of a Normal Esophagus

The normal esophagus in an animal that has been fasted is empty or contains a minimal amount of clear fluid or foam. If the esophagus contains ingesta, a large pool of fluid, or bilious fluid, then gastroesophageal reflux, motility dysfunction, or esophageal obstruction should be suspected.

The feline esophagus is composed of striated muscle in the proximal two thirds and smooth muscle in the distal one third, whereas the canine esophagus is composed almost entirely of striated muscle. Longitudinal folds are found throughout the canine esophagus and in the feline cranial esophagus. In the cat, circumferential mucosal folds in the caudal esophagus form prominent annular ridges (a "herringbone" pattern) that appear endoscopically as a pattern of circular rings. This ringlike appearance is not seen in the dog. The normal esophageal mucosa in cats and dogs is smooth, glistening, and pale pink or grayish pink in color. It is noticeably less red than the gastric mucosa.

GASTROSCOPY

Procedure

The patient should always be placed in left lateral recumbency for gastroscopy. The antrum and pylorus are away from the tabletop in this position, and this significantly improves the endoscopist's ability to completely examine and more readily traverse these structures with the scope. Every patient that undergoes gastroscopy should have a complete examination of all areas of the stomach. It is essential that the beginning endoscopist learn to identify landmarks properly. It is only after familiarity with luminal gastric anatomy is developed that maneuvering the endoscope to obtain a retroflexed view of the cardia, advancing the endoscope around the incisura angularis to reach the antrum, and traversing the pyloric canal become consistent and effortless procedures.

Gastroesophageal Junction

Because the esophagus is essentially in a posterior plane compared with the location of the stomach, the endoscope tip needs to be deflected when it is in the distal esophagus before it can be successfully advanced to the stomach. As the endoscope is advanced to the distal esophagus, the endoscope tip should be centered at the gastroesophageal orifice. The endoscope tip is deflected to the left approximately 30 degrees with simultaneous slight upward deflection as the gastroesophageal junction is passed. This is usually easily accomplished by rotating the outer control knob in a counterclockwise direction for left deflection and by rotating the inner control knob in a counterclockwise direction for upward deflection. In some patients, minimal or no upward deflection is needed. When properly directed there should be no resistance to advancing the endoscope to the stomach.

Proximal Stomach and Gastric Body

The endoscope tip should be positioned just through the gastroesophageal junction so that an overview and orientation within the gastric lumen can be obtained. As the tip enters the stomach, the rugal folds, generally on the greater curvature of the body, will be seen. Often the stomach walls will be partially or completely collapsed, especially in medium to large size dogs or if only a small volume of air was insufflated during esophagoscopy. In this instance the view of the stomach will be quite limited, and it is necessary to pause and insufflate air. Generally the distention should be at least to the point that the rugal folds begin to separate. During insufflation the endoscopist must be careful to not cause **overdistention** of the stomach, since this may result in significant cardiopulmonary compromise. When the stomach is over-distended the rugal folds will be almost completely flattened or not detectable, superficial blood vessels can sometimes be observed, and there may be mucosal blanching. Usually the respiratory rate increases significantly. A sufficient volume of air to moderately deflate the stomach should be suctioned off as soon as possible. During the course of most gastric examinations, both air insufflation and suction are commonly used to maintain a proper and safe balance of distention. Several observations should be made during initial examination of the stomach. These include presence of any fluid or ingesta, ease of distendability of the gastric walls when air is insufflated, and gross appearance of the rugal folds and mucosa.

As the endoscope is gradually advanced through the proximal stomach, the area of the gastric body can be thoroughly evaluated by using the control knobs to deflect the endoscope tip or by rotating the insertion tube with the right hand. With the patient in left lateral recumbency and the endoscope held in a conventional manner (ie, buttons up), the endoscopic view is predictable. The smooth lesser curvature is on the endoscopist's right, and the rugal folds of the greater curvature are seen below and to the left. Usually any required direction changes can be made with the left thumb on the inner control knob and the right hand controlling rotation. Only minor direction changes are usually needed to provide a panoramic view. The endoscope is advanced along the greater curvature until the angulus is identified. The angulus appears as a large fold that extends from the lesser curvature. The angulus is an important landmark that separates the body of the stomach form the antrum. With the patient in left lateral recumbency, the antrum will be directed up or away from the tabletop. The endoscopist must be able to maneuver around the angulus to advance the endoscope to the antrum, pylorus, and duodenum. This is one of the more difficult steps in which to gain proficiency when learning gastroscopy techniques.

Retroversion (J-maneuver)

The importance of the retroversion maneuver is that it provides an en face view of the angulus and the cardia and fundus. On forward view only a tangential view of the angulus is obtained, and the cardia and part of the fundus are not seen at all. Failure to thoroughly examine the proximal stomach may cause lesions such as erosions, ulceration, or neoplasia, or a foreign body wedged in the cardia or fundus to be missed.

To provide an en face view of the angulus, the retroversion maneuver is initiated at a point opposite the angulus. The endoscope is advanced along the greater curvature to the level of the distal body and proximal antrum. The inner control knob is turned counterclockwise with the left thumb, and as the endoscope is gradually advanced, the angulus can be seen en face. There are variations of normal appearance. The endoscope tip is then deflected upward as far as possible (full counter-clockwise rotation of the inner control knob) as the endoscope is simultaneously advanced a little further. Generally, at least 180 degrees of tip deflection will be required for this maneuver. Many newer endoscopes are capable of 210 degrees of upward tip deflection. This further advance provides a retroflexed view of the endoscope as it enters the stomach through the cardia. Pulling the endoscope back once this view is attained draws the endoscope tip closer to the cardia. In cats the retroversion maneuver is started when the endoscope tip is in the mid body area. The tip is deflected upward as the endoscope is advanced. Because of a smaller working area when compared with most dogs, an en face view of the angulus is not usually achieved in cats.

Antrum

The antrum differs from the body of the stomach in that there are no rugal folds, and peristaltic contractions are sometimes observed in the gastric body. To advance from the distal body to the antrum, upward deflection (counterclockwise rotation of inner deflection knob) is applied as the instrument tip is passed along the distal greater curvature. This usually reveals a view of the angulus, and from this position the endoscopist can appreciate the appearance of two separate "tunnels", one on each side of the angulus. The upper area is the gastric body (the first area viewed is the lesser curvature as it extends beyond the angulus), and the more dependent tunnel is the antrum. From this location the retroversion maneuver can be performed, or the endoscope can be advanced to the antrum.

Antral peristaltic waves may be observed when the endoscope is in the mid to distal gastric body. These are seen as round and symmetrical rings that form in the proximal antrum and sweep toward the pylorus as a rolling wave. These contractions are generally not observed in cats unless metoclopramide or cisapride has been administered. When present they usually occur at a frequency of three to four contractions per minute.

Occasionally the endoscopist will encounter difficulty in maintaining the endoscope tip in proper position in the distal antrum to facilitate smooth passage through the pylorus when there are active antral contractions. The pylorus is often persistently closed during periods of antral contractions.

Usually there are no folds in the antrum. Refluxed duodenal bile may be present and in some cases, active reflux can be observed during the procedure. The antrum should be evaluated carefully for presence of mucosal hypertrophy or folds that may result from chronic inflammatory diseases or chronic gastric hypertrophy, polyps, ulceration, and masses. When present, gastric neoplasia commonly involves the antrum and lesser curvature of the body. Adenocarcinoma is the most common malignant tumor in the stomach of the dog, while lymphosarcoma is the most common in the cat.

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FLEXIBLE ENDOSCOPY IN PRIVATE PRACTICE

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There are a number of flexible fiberoptic endoscopes of different makes, lengths, diameters and functions available for small animal endoscopy. Unfortunately there is no one endoscope that can adequately perform all endoscopic procedures (ie, GI endoscopy, bronchoscopy, nasal endoscopy, and cystoscopy). Even within the same procedure endoscope requirements differ based on the great variability in animal size. Selection of an endoscope should be based on specific needs, cost constraints, and on the intended uses. In small animal veterinary medicine versatility is an important factor and the endoscope selected should be able to perform as many functions as possible. All too often the financial factors become the major determinant in endoscope selection. Purchasing an inferior endoscope may save money in the beginning but probably not in the long run. The inexpensive endoscopes generally have poor optics and awkward handling characteristics and suboptimal construction or durability resulting in user frustration and poor diagnostic capabilities; consequently these endoscopes often collect dust in the storage cabinet. Most endoscopists recommend purchasing a quality instrument and that in the long run it should pay for itself over several years due to the good diagnostic capabilities and increased use. With appropriate instrument care an endoscope can last for many years.

FIBEROPTICS

All current endoscopes incorporate fiberoptics in their construction. Fiberoptics are bundles of glass fibers that function in transporting light or images around bends. Fiberoptics are unique in that they do not transmit heat but only light. Fiberoptics also transmit images but to do so the glass fibers are coherently packed together into tight bundles to transmit an image. The size of individual fibers, compactness of fiber bundles and accuracy of coherent bundle relationship determine the sharpness of the image and consequently the expense of the endoscope. The average glass fiber is 8 to 12 microns in diameter with up to 40,000 fibers in one bundle.

Fiberoptic glass bundles are very fragile and can be easily damaged. Broken fibers in the image transmission bundle will cause black dots to appear in the image. Damage to the illumination fibers will simply result in less light transmission.

FIBEROPTIC ENDOSCOPIC ANATOMY

There are two basic type of endoscopes available for gastrointestinal and respiratory endoscopy; fiberoptic endoscopes and video endoscopes. Fiberoptic endoscopes transmit both light and images that are viewed in the hand piece of the endoscope. A video camera can be attached to the optics for viewing on a monitor. Video endoscopes have fiberoptics for illumination but also contain a small microelectric video-chip located in the distal end of the insertion tube. The image is then transmitted electronically from the chip through a video processor to a television monitor where the image is viewed. Although more expensive than the fiberoptic endoscopes, these endoscopes provide a clear sharp image making it easier to manipulate the endoscope in the patient.

The fiberoptic endoscope consists of several sections: the insertion tube, hand piece and umbilical cord: The **insertion tube** is flexible and comes in different lengths and diameters. In addition to the fiberoptics the insertion tube also contains a suction-biopsy channel and GI endoscopes also an air or water channel. The distal end is attached by cables to the control knobs in the hand piece for distal tip deflection. The **hand piece** is the portion of the endoscope that contains the control mechanism and houses the eyepiece for visualization. Housed in the hand piece are the control knobs for up/down angulation and right/left angulation of the distal tip. The air-water valve is located in the hand piece and when light pressure is applied to the valve forces air through the endoscope for insufflation. Depression of the valve results in a water spray onto the endoscope lens for cleaning purposes. Depression of the suction valve results in suction of gas or fluid through the operation channel. There is a separate operating channel opening in which forceps or other instruments can be passed but they must travel down the section tube. It should be noted that suction is not possible when instruments are in the operating channel. The **umbilical cord** of the endoscope conveys light from the light source via fiberoptic bundles and also contains a suction tube and air/water tube. An endoscopic light source is required and options include high intensity halogen or xenon light sources of 150 or 300 watts. The higher wattage provides greater illumination and zenon is reported to provide truer color. Endoscopic light sources also contain an air pump necessary for insufflation of the GI lumen. A suction source is necessary for endoscopy but is not usually part of the endoscopy light source system.

ENDOSCOPE SELECTION

The insertion tube characteristics and distal tip deflection (two way vs. four way) are the major determinants in endoscope selection. See Table 1 for a description of various types of endoscopes, their characteristics, and use.

Gastrointestinal endoscopy requirements for dogs and cats are as follows. The insertion tube size will vary based on the size of the patient. The standard insertion length of most human upper gastrointestinal endoscopes is 100 to 110 cm. This length is adequate for cats and small to medium size dogs, but often too short to reach the duodenum in animals over 30 kg. In larger dogs a length approaching 130 to 145 cm is needed for duodenal evaluation. The longer small diameter endoscopes are veterinary specific. Also the outside diameters of 7 to 9 mm are ideal for passage

Table 1. Types of Endoscopes, Their Characteristics, and Use

TYPE	DIAMETER	LENGTH	BIOPSY	COMMENTS
Human GI Endoscopes	7.9–12 mm	100–110 cm	2.8 mm	Too short for large dogs, some too large a diameter for small animals
Human Slim GI Gastroscopes	4.9–6 mm	75–110 cm	2.0–2.2 mm	Ideal for small animals, for bronchoscopy in large dogs, has smaller biopsy channel
Veterinary GI Endoscopes	7.9–9.0 mm	140–145 cm	2.2–2.8 mm	Ideal for all but the smallest animals
Human Bronchoscopes	4.0–5.9 mm	55–65 cm	2.0 mm	Too short for large dogs, too a large diameter for small animals
Veterinary Bronchoscopes	5 mm	85 cm	2.0 mm	Ideal for bronchoscopy except small dogs and cats
Specialty fiberscopes	2.9–3.5 mm	75–100 cm	1.2 mm	Bronchoscopy in small animals, urinary in male dogs, very small channel

through the pylorus. Smaller diameter Gi scopes 4.9 to 6 mm and approximately 75 to 100 cm in length work very well for cats and small dogs. These endoscopes have a smaller size biopsy channel (2–2.2 mm). The ideal gastrointestinal endoscope should have 4-way distal tip deflection with at least 180 degrees and preferably 210 degrees upward deflection of the distal tip. Endoscopes having only two-way deflection are not recommended for GI endoscopy. Most two-way deflection scopes are used for respiratory and urinary evaluation and will not have an air water channel. Human duodenalscopes and colonoscopies, although longer in length, are larger in diameter (>10 mm) and are not recommended.

Respiratory endoscopy for bronchoscopy in small animals has several options. Bronchoscopes have two-way deflection and are without an air water channel. The human bronchoscopes are however too short (approximately 55–65 cm) for large dogs and too large in diameter (4–5.9 mm) for cats and small dogs. The reason they are too short is the fact that the human trachea is much shorter when compared to a 30-kg dog. Some veterinary bronchoscopes are of smaller diameter and longer in length. Alternate endoscopes include the shorter human slim GI endoscopes 5–6 mm diameter and 75–100 cm in length. In cats and very small dogs the thin diameter bronchoscopes or urinary scopes must be used for bronchial evaluation. Small diameter flexible endoscopes are also used to evaluate the posterior nasal pharynx and can be used for nasal endoscopy however rigid endoscopes are recommended for this purpose.

Endoscopic Accessories

There are a wide variety of accessories that are available to pass through the operating channel. There are however a number of essential instruments including biopsy forceps, foreign body removing instruments and cytology brushes and aspiration tubes.

There are several types of tissue biopsy forceps including standard oval cup, fenestrated oval cup, and alligator forceps. The fenestrated cup forceps do not cause as much crush artifact and tend to give good samples. The alligator type forceps are thought by some to give larger tissue samples because they tend to tear tissue but it may be associated with considerable crush as well. Both types of forceps are available with a central needle or spike that tends to anchor the forceps into the mucosa preventing them from sliding down the tissue. The biopsy forceps should be kept clean, sharp and well lubricated.

Biopsy forceps should never be used for foreign body retrieval. Several types of grasping forceps and retrieval baskets are available for foreign body removal. Three basic graspers are the 3- or 4-pronged wire forceps, the “rat tooth” forceps and the “duck bill” type forceps. The pronged forceps are useful for large irregular objects, the rat tooth for grasping fabric or other soft material and the duck bill for flat objects like coins. Wire baskets either 3 or 4 loops are required to remove large objects like rocks. I would recommend two different foreign body retrieval instruments; a two or three pronged grasping forceps and a foreign body retrieval wire basket. With these two instruments most foreign bodies can be removed.

Aspiration tubes are useful for suction of fluids. For bronchoscopy and bronchial alveolar lavage aspiration tubes are often used however lavage can also be performed directly through the biopsy suction channel of the endoscope. Small brushes are available for brush cytology for both the GI and respiratory system.

ENDOSCOPE CARE

Following the endoscopic procedure it is important to adequately clean the endoscope for disinfection and to maintain proper endoscope function and equipment life span. It is advised to follow the manufacturer's instructions. We routinely use an enzymatic cleaner followed by Nolvasan® solution to disinfect the scope. It is important that the biopsy/suction channel be adequately brushed and clean. It is usually not necessary to completely sterilize the endoscope. We will sterilize our bronchoscope if a resistant bacteria is cultured from the patient.

Ancillary instruments such as biopsy forceps and foreign body graspers should be clean. Blood, mucous or other secretions dried on the forceps will often "freeze" the forceps so they are not functional. Following cleaning they should be lubricated with silicone or mineral oil. Others suggest using vegetable oil for lubrication. Ultrasonic cleaners work well in cleaning biopsy forceps. The endoscope should be stored in a hanging position in a cabinet rather than in the packing case they came in. This allows for drainage and drying of the scope as well as the ability for the insertion tube to be in a straight position. Forceps should not be hung until dry because if hung wet, fluid and secretions will drain to the forceps tips and can freeze them close.

INDICATIONS AND TECHNIQUE

The basic indications for diagnostic endoscopy are for a visual examination of an area, to biopsy tissue, cytology procurement, and fluid aspiration. Operative procedures performed include foreign body removal, gastrostomy tube placement, esophageal stricture removal, and polyp removal.

The actual technique of endoscopy is beyond the intent of this article. There are some basic principles, however, that one should keep in mind while performing endoscopy. I believe it is important to maintain orientation of the endoscope so when moving the distal tip up it actually moves up on the monitor. One should never force the endoscope and should only pass the scope as one sees the lumen. If the operator is “lost” the endoscope should be withdrawn until the operator can determine where they are and then re-advance the endoscope.

When performing GI endoscopy it is important to avoid over-distention of the stomach or intestine. An over-distended bowel can hinder respiration and abdominal venous return and will also make tissue biopsy more difficult because the mucosa is stretched tight.

SUMMARY

Endoscopy can be an excellent diagnostic tool in veterinary medicine. To become successful at endoscopy it is important to first take a basic training course and to then practice the technique. One should always consider “will endoscopy would be useful in a specific case work-up?”

ENDOSCOPY OF THE SMALL AND LARGE INTESTINE

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Endoscopy is a minimally invasive technique that permits visual inspection of the esophagus, stomach, proximal small intestine, colon, and sometimes the distal ileum. Lesions can be characterized by their severity and extent. Furthermore, it allows sample collection for histopathologic, cytologic, and microbiologic evaluation. The primary indications for gastroduodenoscopy are the evaluation of chronic vomiting, hematemesis, melena, and chronic diarrhea. Colonoscopy is used to investigate chronic diarrhea, fecal incontinence and dyschezia, persistent hematochezia, fecal mucus, and tenesmus. Endoscopy is contraindicated only in patients that are unsafe for anesthesia, who are suspected of gastrointestinal perforation, or are poorly prepared.

Ideal preparation for gastroduodenoscopy requires a 24-hour fast. A longer period is required if delayed gastric emptying is suspected (vomiting of undigested food >12 hours after ingestion). Adequate preparation of the colon requires a 48-hour fast and the administration of a gastrointestinal lavage solution (GoLYTELY®, NULYTELY®, COLYTE®). These solutions contain polyethylene glycol as a non-absorbed solute and are administered two to three times, 2 to 6 hours apart on the day prior to colonoscopy at a dose of 30 to 40 mL/kg. Stomach tubing or nasogastric intubation is required. Oftentimes a warm water enema (20 mL/kg) just prior to the procedure is required to clean the distal colon and rectum. Large cotton tipped applicators (Scopettes®) are used to clean the colon after the enema. Enema preparation results in poor cleaning of the proximal colon and may produce mucosal artifacts (erythema and bleeding) if used alone. Routine endoscopy is performed with the patient in left lateral recumbency. This enables the examination of the pylorus and ileocolic region allowing drainage to the gastric body and descending colon.

Successful gastroduodenoscopy and colonoscopy requires an endoscope has a working length of at least 100 cm with an insertion tube diameter of less than 10 mm and a 2.8 mm biopsy channel/instrument channel diameter. The tip of the endoscope should be capable of at least 180 to 210 degree deflection in one direction and 90 to 100 degrees in the other three. Smooth or serrated biopsy instruments with oval or round cups without a spike are preferred for biopsy collection.

Passing the endoscope through the pylorus is the most difficult part of the gastroduodenoscopic study but is necessary for thorough evaluation of the upper gastrointestinal tract as the duodenum is frequently a site of pathology. Oftentimes the initial examination of the stomach is cursory while trying to traverse the stomach without excessive air insufflation which increases pyloric tone. This is accomplished by following the rugal folds to the antrum. Once in the antrum the pylorus is usually visible and centrally placed. However sometimes it may be obscured by folds of mucosa or may be positioned eccentrically (especially to the left). The endoscope should be advanced slowly maintaining the pylorus in the center of the field of vision. This is accomplished by a combination of up-down manipulations and torquing the insertion tube of the scope. Occasionally manipulation of the left-right deflection is required to maintain the ideal position of the scope tip. Torque is a technique that lessens the endoscopist's reliance on the left-right deflection. It is initiated by rotating the insertion tube with the hand piece following (not vice versa) and allows the endoscopist to benefit from the greater bending capability of the up-down deflection. This technique becomes difficult when the scope is buried deep within the patient (increased resistive forces) or when the distal end of the scope is fixed (after pyloric intubation). As the endoscope moves within approximately 3 mm of the pylorus clear vision is lost and can only be appreciated as a dark area (pyloric canal). This dark area should be kept in a central location, and gentle consistent pressure should be used to advance the endoscope. Once the tip of the endoscope touches or enters the pyloric canal, insufflation of air and deflection of the scope downward and to the right can facilitate passage through the pylorus and beyond the cranial duodenal flexure. During this time the endoscopist will appreciate the redder duodenal mucosa sliding by the tip of the endoscope. Later, after a few centimeters, the endoscope can be centralized and a luminal view of the descending duodenum can be obtained. Repositioning the patient in dorsal or right lateral recumbency may help if the pylorus cannot be properly aligned. Administration of glucagon, metoclopramide or atropine and avoidance of narcotic premedication have all been suggested to ease pyloric intubation. If the pylorus cannot be entered, the biopsy instrument can be passed through the pylorus and blind biopsies collected. This, however, increases the risk of perforation and the cost benefit ratio should be weighed closely.

The normal duodenal mucosa is redder, granular and more friable than the stomach. Submucosal vessels are not apparent. Careful examination of the proximal duodenum may show the duodenal papillae (two in the dog and usually one in the cat), which appear as white protuberances. Linear trauma is often seen and is a result of trauma from the endoscope and should not be mistaken for pathology. Peyer's patches are seen in the canine duodenum and appear as pale, oval depressions in the mucosa. The endoscope should be advanced as long as a luminal view can be maintained. In large dogs only the descending duodenum can be seen whereas in small dogs and cats the proximal jejunum may be reached. A diseased duodenum is recognized by increased granularity and friability (bleeds freely when contacted with the endoscope). The degree of granularity should be assessed with the duodenum fully distended. Lymphangiectasia is heralded by lipid-filled villi or multiple discrete lipogranulomas. Other abnormalities include erosions, ulcerations, erythema, masses or parasites. Usually the best views of the gastrointestinal tract are obtained as the endoscope is withdrawn. After thorough examination of the small intestine and stomach, the endoscopist should suction the insufflated air to decrease the risk of gastric dilation/volvulus.

Samples collected in the duodenum include aspirates for *Giardia* identification and/or anaerobic/aerobic cultures for determination of small intestinal bacterial overgrowth, and brush cytology of mass lesions. Deep biopsy samples can be obtained at the anatomical flexures (cranial and caudal flexures) where biopsy instrument is orientated perpendicular to the mucosal surface. This increases the likelihood of obtaining lamina propria rather than villus tips. With mass lesions the same site can be repeatedly biopsied to gain "deep" samples. Ulcers should be biopsied at their periphery to avoid perforation and sampling necrotic debris present in the ulcer bed. Appropriate pressure from the biopsy instrument on the intestinal wall can be determined by movement of the intestine away from the tip of the endoscope or by bending of the biopsy instrument. Further pressure risks perforation. Multiple samples (>8) are required to ensure the surgical pathologist is provided with an adequate amount of representative tissue (preliminary data from one study suggests 40% of samples contain a lesion). The biopsy samples are directly transferred from the biopsy forceps to a saline moistened histopathology cassette sponge (filter paper can be substituted). The sample can usually be "wiped" onto the sponge. Teasing with a needle to dislodge the biopsy can cause tissue damage. The sponge is placed in a pencil labeled cassette and fixed in 10% formalin.

Endoscopic evaluation of the rectum and colon can be achieved with either a flexible or a rigid endoscope. Rigid endoscopes (adult 17-mm diameter or pediatric 9-mm proctosigmoidoscopes) allow visualization of the rectum and descending colon with their 25-cm working length. Flexible endoscopes allow evaluation of the rectum, colon, and sometimes the distal ileum. General anesthesia is recommended for colonoscopy while heavy sedation may suffice for proctoscopy.

Before colonoscopy, a digital examination of the rectum and anus is recommended to detect anal lesion not easily identified by endoscopy (perineal hernias, anal sacculitis). Afterwards the tip of the lubricated endoscope is introduced and the bowel is insufflated to obtain a luminal view. The distal rectum may need to be "straightened" with the endoscopist's index finger if a luminal view is not apparent. The endoscope is advanced along the descending colon to the left colic flexure. Continuous insufflation of air and an assistant closing the anus may be required to distend the colon and maintain a luminal view. Fecal material can be cleared from the tip of the endoscope by depressing the air/water button or touching the tip of the endoscope to clean mucosa. Excessive enema solution can be aspirated with suction. Typically a luminal view cannot be maintained when passing the left colic flexure because of its acute angle. The slide-by technique is employed where the tip of the endoscope is oriented in the perceived direction of the flexure and then gently advanced for a few centimeters until a luminal view is once again possible. The slide-by is named for the impression of the mucosa sliding by the tip of the endoscope. With passage into the transverse colon the endoscopist may encounter the right colic flexure; however, it is often "straightened" by the endoscope. The ileocolic valve is a button-like protuberance lying alongside the cecum (seen as a blind ending pocket). If the ileum is entered the tip of the endoscope should be centralized within the lumen of the sphincter and the endoscope advanced using gentle pressure and air insufflation. Like the small intestine, the best views of the colon are made while withdrawing the endoscope with air insufflation. Finally, the terminal portion of the rectum can be examined with tip of the scope in a retroflexed position. Suction of air from the colon is not required.

The normal colonic mucosa is smooth, pink and submucosal blood vessels are seen. Small 1- to 3-mm lymph follicles are seen in the rectum and cecum. Diseases that infiltrate the lamina propria (eg, lymphoma, inflammatory bowel disease) often obscure submucosal blood vessels. There should be no evidence of ulceration or erosions in a normal colon. Bleeding from endoscope passage may be interpreted as increased friability. Masses, strictures, parasites, and excess mucus signal disease.

More than eight biopsies should be collected from the colon in the same fashion as those in the duodenum (90 degree angle between biopsy instrument and mucosa with numerous areas sampled). Cytology is useful for the identification of *Histoplasma* spp, *Prototheca* spp, *Campylobacter jejuni, Clostridium perfringens*, and for the presence of neutrophils and neoplastic cells.

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SPECIAL GI ENDOSCOPY TECHNIQUES — FOREIGN BODY RETRIEVAL & GASTRIC FEEDING TUBE PLACEMENT

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PERCUTANEAOUS ENDOSCOPIC GASTROSTOMY (PEG) TUBE PLACEMENT

Gastrostomy tube feeding is indicated for long-term (> weeks) nutritional support of an anorectic or dysphagic patient. In addition, gastrostomy tubes have been used in difficult to medicate pets and those requiring supplemental fluids (eg, chronic renal failure). Gastrostomy tube diameter (18–24 Fr) allows the administration of blended pet foods and medications mixed into slurries. Contraindications include vomiting, mental depression, gastrointestinal obstruction (all increase the possibility of aspiration), and conditions which the stomach cannot be apposed to the body wall (ascites, masses, and adhesions).

A variety of gastrostomy tubes are available; silicone catheters (Global Veterinary, US Endoscopy), polyurethane (MILA International), and Latex (BARD Urological Division). Catheters are typically modified by cutting two 2- to 3-cm sections from the proximal, open end of the tube. The first section has a small stab incision made centrally and is passed over the length of the tube to a position adjacent to the mushroom tip; this serves as an internal flange. The second section, with a similar incision, is positioned after tube placement, adjacent to the body wall, to serve as an external flange. These flanges when positioned help prevent the displacement of the gastrostomy tube. Passage of the tube through the stomach and body wall is facilitated by a micropipette, which serves as a sharp leading edge to the tube assemblage and protects the leading suture from inadvertently being severed when being drawn through the body wall.

After the patient is anesthetized and placed in right lateral recumbency the area just ventral to the left 13th rib is clipped and surgically prepared. The endoscope is introduced into the stomach and carefully inflated until the abdomen is distended. The site of tube placement is determined by transillumination and by palpation by an assistant to ensure the spleen is not interposed between the greater curvature of the stomach and the left body wall. A small stab incision is made through the skin and a 14- to 18-gauge, 1- to 2-inch, over-the-needle intravenous catheter is passed into the stomach. The needle is removed from the catheter and a generous length (approximately two times the length of the mouth to the last rib) of 1-0 or 0-0 nylon suture material is passed through the catheter into the stomach. The suture is grasped with a rat-tooth endoscopic retrieval instrument and withdrawn from the patient through the esophagus and mouth. The suture material is then grasped and threaded through a micropipette (tapered tip first) and anchored to the gastrostomy tube by placement through an 18- to 20-gauge needle pre-placed transversely through the tapered open end of the tube. The gastrostomy tube assemblage is completed by securely knotting the suture to the tip of the tube. The suture material is grasped at its point of exit from the abdominal wall and traction is applied to draw the entire catheter assemblage through the lumen of the oral cavity, esophagus, and stomach. At this time resistance is met by the tip of the tube (resting against the stomach wall) and by the internal flange (upper esophageal sphincter). Firm traction and digital manipulation (of the mushroom tip/internal flange) allows the gastrostomy tube to be passed through the body wall with the distal flanged end resting against the gastric wall (which is now in apposition with the body wall). The external flange is then passed over the tube resting beside the body wall and the position is marked with indelible ink. The final position is checked by reinserting the endoscope into the stomach. The internal flange should not cause blanching of the gastric mucosa and the position of the external flange should allow the tube to be "spun." If the gastrostomy tube is too tight ischemic necrosis of the gastric or body wall may ensue. Finally a jacket (two holes for front legs) made from stockinette is placed over the tube for protection from vandalism.

Complications related to gastrostomy tube placement are rare but include splenic laceration, gastric hemorrhage, and pneumoperitoneum. Delayed complications and those related to enteral feeding include gastric and body wall pressure necrosis, displacement of the feeding tube, aspiration, tube obstruction and leakage from the gastrostomy site. The incidence of most of these complications can be diminished by accurate gastrostomy tube placement and fixation. Gastrostomy tube obstruction is usually the result of owners neglecting to flush the tube with water after feeding although tube kinking, tablet lodgment or precipitated medications can be a cause. Tube obstructions can be remedied by flushing with warm water or carbonated water that has been allowed to sit for an hour. For more stubborn blockages incubation with pancreatic enzymes/meat tenderizes or the passage of a stylet wire has been advocated. A mild amount of leakage from the gastrostomy site is expected for the first few days after tube placement. Persistent or increased amounts of discharge can be related to tube dysfunction, infection, or because the stoma site is too large. Local infections can be treated with cleaning (dilute betadine or chlorhexidine) and topical antibiotics. The gastrostomy tube position can be checked by injecting 3 to 5 mL iohexol through the tube and making a radiograph. Fasciitis is heralded by marked local swelling, erythema, discharge, and systemic signs of inflammation. Treatment includes aggressive intravenous antibiotic administration and often surgery. Displacement of the feeding tube is most common in larger breed dogs and relates to the stomach "falling off" the end of the gastrostomy tube. This is further complicated by the delivery of food to the peritoneal cavity and resultant peritonitis. Some authors recommend the placement of percutaneous gastrostomy tubes only in dogs under 30 kg bodyweight.

Percutaneously placed gastrostomy tubes should be left in place for a minimum of 14 days. In patients receiving chemotherapy, immunosuppression, or with advanced malnutrition/debilitation a longer period is required. Tube removal can be facilitated in a number of ways. In larger dogs the tube can be cut at the body wall allowing the internal flange and mushroom tip to be passed through the gastrointestinal tract. In small dogs/cats the mushroom tip can be flattened with a stylet and then withdrawn leaving the internal flange to pass or preferably the tube can be cut at the body wall and the mushroom tip/internal flange retrieved endoscopically. After withdrawal the gastrocutaneous tract should seal with minimal leakage within 24 hours.

FOREIGN BODY RETRIEVAL

Gastrointestinal foreign bodies are commonly seen in dogs less frequently in cats. Dogs tend to have indiscriminate eating habits, swallow of incompletely masticated food and are more apt to play with toys. Foreign body ingestion may result in anorexia, regurgitation, odynophagia, excess salivation, vomiting, diarrhea from complete or partial gastrointestinal obstruction or from gastrointestinal trauma during passage. Foreign bodies may be managed by conservative, endoscopic, or surgical mean. Sequential radiographs documenting movement of the foreign body, and the absence of clinical signs allow conservative management. If the foreign body is large, pointed, suspected to be toxic (eg, Zn pennies) or caustic (eg, batteries), or the animal has clinical signs, or movement cannot be documented, endoscopic or surgical extraction is indicated. The diagnosis of a GI foreign body is usually confirmed by radiographic evaluation (radiodense object, esophageal, gastric or intestinal distention are typical). If the foreign body is suspected of gastrointestinal perforation surgery, not endoscopy is required. Linear foreign bodies and small intestinal or esophageal obstructions are considered emergent cases because the longer they are in situ the greater the damage to the wall of the gastrointestinal tract.

Common esophageal foreign bodies include fish hooks, bones, Greenies™, rawhide chews, toys, and hairballs which tend to lodge at the thoracic inlet, heart base, or diaphragmatic hiatus. Small dogs (<5 kg) are at risk. Presenting complaints of esophageal foreign bodies include halitosis, odynophagia, ptyalism, regurgitation, anorexia and increased respiratory rate (pneumonia and pain). Most esophageal foreign bodies can be successfully removed endoscopically or, at least, pushed into the stomach to expose the foreign material to gastric acid or for easier surgical access. Surgery of the esophagus should be avoided because of poor healing, difficult access, and morbidity.

Greenies are toothbrush-shaped dental chews that are commonly implicated in esophageal obstructions. Evidence suggests that they are hard to remove endoscopically, cause more severe esophageal damage, and result in higher mortality rate and stricture formation compared with other causes. Hopefully, this situation has been addressed by reformulation (August 2006) to New Greenies™.

Retrieval equipment should include through-the-endoscope instruments such as a snare, basket retrieval instrument, 3- or 4-pronged or rat tooth graspers. In addition a large rigid grasping instrument (eg, laparoscopic grasper), which can be passed alongside the endoscope, is useful for proximal esophageal foreign bodies. Fishhooks should be surgically removed if perforation is suspected (pneumomediastinum). To avoid a surgically created esophageal wound, the surgeon can remove the barbed end of the hook lying outside the esophagus after which the endoscopist can remove the remainder of the hook. If a more superficial location is suspected then the fish hook can be grasped and gently withdrawn. Damage to the mucosa and submucosa will heal quickly. Radiographs should be repeated after removal of an esophageal foreign body to assess for mediastinitis and pneumomediastinum. The sensitivity of the radiographic study can be enhanced by placing 2 to 10 mL of iohexol in the esophagus. Small perforations (<1 cm) can be managed medically (gastrostomy tube and intravenous [IV] antibiotics) while larger rents required surgery. If the foreign body caused esophageal trauma especially circumferential trauma predisposing the patient to stricture formation, short-term medical management is required. A combination of medications to decrease gastric pH (eg, omeprazole 0.3 mg/kg q24h, ranitidine 2 mg/kg q8h, or famotidine 0.5 mg/kg q12h), increase lower esophageal sphincter tone (metoclopramide 0.2 to 0.4 mg/kg q8h or cisapride (0.3 to 0.5 mg/kg q8h), and coat ulcerated areas (sucralfate 1 g/25 kg q8h) can be used. Severe trauma may require the placement of a percutaneous gastrostomy tube. Esophagoscopy should be repeated in 7 to 10 days to asses for stricture formation.

Gastric foreign bodies are often discovered incidentally with radiology. Other patients present for the investigation of vomiting or anorexia. Gastric foreign bodies are easier to remove than esophageal foreign bodies because of the increased room allowing easier endoscopic manipulation. When the patient is in left lateral recumbency they are often located in the cardia as the endoscope enters the stomach. A wide variety of objects are seen because of the indiscriminant eating behavior of some dogs. When retrieving large gastric foreign bodies negotiating the lower esophageal sphincter can be difficult because they have the tendency to "fall off" the retrieval instrument. Holding the foreign body as close to the endoscope as possible and insufflation with air during slow steady withdrawal will give the endoscopist the best chance of success. Using a snare or basket rather than grasping instruments also gives better results. If the patient is referred from another hospital another set of radiographs should be made to determine the presence of food in the stomach (which hinders retrieval and increases the risk of aspiration), to determine the presence of perforation (decreased serosal detail) and/or to asses whether the foreign body has transited to the small intestine.

Morbidity associated with successful foreign body retrieval is low and most patients can be discharged a few hours after the procedure.

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UNDERSTANDING CRUELTY TO ANIMALS: WHO ABUSES ANIMALS AND WHY?

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Professionals in law enforcement, animal care and control and veterinary medicine are increasingly asked to respond to situations of serious and often violent cases of animal cruelty. Effective response to animal abuse and neglect requires more than a recognition of the physical signs of non-accidental injury and neglect. It also requires an understanding of the some of the motivations underlying these acts. This can be challenging for responders who need to be able to temporarily "think like an abuser" to understand the actions that may have produced the situation that is presented to them.

Timely response to animal cruelty is increasingly being seen as a high priority. Society is looking for new tools and resources to employ in efforts to combat violence, including identifying real or potential perpetrators at an early age and defining actions that might prevent violent behavior. One idea that is attracting greater attention as a source of insight into the dynamics of violence is the long- standing belief that the treatment of animals is closely associated with the treatment of fellow human beings. Although the concept has a long intellectual history, scientific and scholarly attention to the idea has been relatively limited.[1,2,5] Cruelty to animals represents an objectively definable behavior that occurs within a societal context. It provides an opportunity to measure the interaction of the actions an individual is intrinsically capable of performing and the actions his/her environment have allowed or encouraged. That the definition of animal cruelty is so strongly influenced by cultures and subcultures need not be a confounding variable, but rather an opportunity to try to unravel the many influences that can shape violent behavior.

THE ECOLOGY OF VIOLENCE AGAINST ANIMALS

Because animal cruelty has traditionally been seen as a minor crime, basic quantitative information as to the nature and extent of animal cruelty has been limited. Good criminological analysis often starts with a solid "victimology" and Vermeulen and Odendaal provide important first steps in filling the void in our knowledge of who victimizes whom.[6]

Animal cruelty is defined differently in every state, but it can fall into several broad categories, each of which may involve different laws and require a different response and possible involvement of veterinary professionals.

SIMPLE NEGLECT

Most reported cases of animal cruelty involve failure to provide adequate food, water, shelter or veterinary care to one or a few animals. Usually these are handled by local animal care and control or humane agencies in an effort to educate the offender to provide proper care. Veterinary professionals play an important role in educating clients and the general public about the basic requirements for animal care. If education proves ineffective, action may be taken under local ordinances. However, cases involving large numbers of animals or which cause death or serious debilitation of animals may be charged as serious misdemeanor or even felony offenses.

GROSS, WILLFUL, CRUEL OR MALICIOUS NEGLECT

A growing number of states make a distinction between simply failing to take adequate care of animals and intentionally or knowingly withholding food or water needed to prevent dehydration or starvation. Although some states fail to recognize neglect as meeting the level of *intentional* cruelty, others treat *any* act, omission or neglect that results in unnecessary or unjustifiable suffering as a potentially serious offense.

Community standards for what is considered to be a reasonable level of care for companion animals have been rising steadily in recent years as veterinary and humane professionals have provided extensive information on proper responsible pet care.

INTENTIONAL ABUSE, TORTURE

Cases of intentional cruelty are the ones of greatest concern to the general public and the ones more likely to involve juvenile offenders. There is legitimate fear that the individuals involved in violent acts against animals present a danger to the public that must be addressed. Intentional animal abuse is often seen in association with other serious crimes including drug offenses, gang activity, weapons violations, sexual assault and domestic violence and can be one of the most visible parts of an entire history of aggressive or antisocial behavior. Such cases are often easier to prosecute than neglect or hoarding cases since the effects of the crime on the victim may be easier to document and the intentionality of the offense is more clearly recognized.

These acts can be the most difficult to understand for professionals dedicated to preventing and relieving animal suffering. It is easy to dismiss the acts as simply being the consequence of poor character or, in the terms of some cruelty laws—"a hardened heart." Psychologists and sociologists have enumerated many potential motives for intentional harm to animals—too many to explain in detail here. But it is helpful to review the range of causes that can lead to such acts. These include:

- **Need for power or control.** This is particularly common in the context of animals killed or injured as part of the perpetration of domestic violence
- **Ignorance of behavior and misreading of cues.** Some instances of cruelty may result from a lack of understanding of animal communication, as in cases

where an animals exuberant approach is misread as a threat, leading to injury to the animal

- **Revenge, retaliation or blackmail.** These cases may involve harm to animals as a way of getting back at neighbors or family member.
- **Imitation.** Children or young adults may imitate the mistreatment of animals they have seen perpetrated by adults, or violence that has been directed to them or their siblings.
- **Peer pressure/ group membership.** Engaging in animal cruelty can be a way of demonstrating a rejection of mainstream societal values that embrace kindness to animals.
- **Deviant arousal.** Animal cruelty, particularly when directed to cats or involving bestiality can be related to various forms of deviant arousal.
- **Curiosity and exploration.** Like curiosity firesetting, some animal cruelty in juveniles may be motivated more by a desire to see what can happen and a lack of recognition of animals as creatures capable of pain and suffering.
- **As means of avoiding/denying attachment.** Some young offenders cause death or harm to animals they profess to love as a way of denying the impact that others are having on them and as a way of rehearsing violent acts they may be contemplating against loved ones.

ANIMAL HOARDING

Animal care and control and law enforcement agencies are reporting a growing number of cases that involve large numbers of animals (often several hundred) kept under extremely poor conditions, often resulting in the death of many animals from disease and starvation. Such cases present substantial challenges for prosecutors and responders due to the large number of animals involved, the possible mental health issues surrounding the defendant(s) and the extremely high recidivism rate seen with this particular offense.

The prosecution of animal hoarding cases can sometimes be unpopular if the defendant is seen as sympathetic and caring, rather than as someone who has caused substantial suffering to a large number of animals. Animal care and control and veterinary professionals can be extremely helpful in educating the public and the triers of fact to the real impact of these actions on the animals involved. Although most prosecuted animal hoarding cases result in convictions or pleas, these cases are notoriously difficult to resolve. Hoarders who are required to make restitution for veterinary costs rarely comply. Those who are ordered to undergo psychological assessment and/or treatment also generally fail to comply.

Many agencies have begun to promote a task force approach to respond to hoarding situations. Such groups involve representatives of all stakeholders in the community, including law enforcement, human health and social services, public health, zoning, code enforcement, and animal protection groups to bring a coordinated effort to these cases. Conviction on animal cruelty charges and probation that allows long-term monitoring can be important tools for such task forces for preventing recidivism of hoarding.

ORGANIZED ABUSE—DOGFIGHTING, COCKFIGHTING

"Blood sports" such as dogfighting and cockfighting have been singled out for special attention in the anticruelty laws of the United States and the United Kingdom since their inception in the 19th century. These crimes continue to flourish, often in connection with other offenses. The lucrative and underground nature of these offenses, and the logistical problems of dealing with many defendants and many animals that may be seized as evidence, can present unique challenges to police, prosecutors and veterinary professionals.

Other forms of "bloodsport" are beginning to attract legislative and legal attention as well. "Hog-dog" competitions in which dogs are pitted against confined hogs have recently been outlawed in Alabama and similar restrictions have been proposed in other states.

RITUALISTIC ABUSE

The phrase, "occult and ritualistic animal abuse," immediately evokes many disturbing images: a cat nailed to a crucifix and burned, the head of a dog left on the steps of a building with a piece of paper bearing a curse stuck in the animal's mouth, a goat's throat slit as part of a ritual sacrifice. Few other crimes against animals create such intense concern within a community. Most crimes in which animals are killed or mutilated and left where they will be discovered immediately raise fears of "satanic" or cult activity and concern about what other crimes the perpetrators of such acts may have committed or be capable of. Yet it is precisely because of the highly emotional nature of these crimes that there is an even greater need for careful, rational, systematic investigation of the evidence and care in prosecution.

ANIMAL SEXUAL ASSAULT (BESTIALITY)

Sexual contact with animals was once subsumed within "crimes against nature" laws in nearly every state. Over the last several decades the repeal of many of these laws through legislative or court action has had the unintended effect of decriminalizing animal sexual assault unless the act involved some other crime such as cruelty to animals, indecent exposure, trespass, or breaking and entering. In response to this unintended change, many state legislatures have reenacted provisions specifically targeting bestiality as distinct from other traditional "crimes against nature" or animal cruelty offenses. These laws continue to change rapidly, but the majority of states have reinstated such provisions. Opponents of such laws maintain that their behavior constitutes a lifestyle choice, analogous to other nontraditional sexual orientations, but this view is countered by the prevailing legal, legislative, and societal view that such contact constitutes "interspecies sexual assault" and is problematic because (1) human–animal sexual contact is almost always coercive,

(2) such practice often causes pain or death for the animal, and (3) animals are unable to consent to or communicate about their abuse.

Prosecutions for animal sexual assault are rare, but they can present unique challenges to prosecutors and often require expert veterinary and psychological testimony

VETERINARY TESTIMONY

Reports and testimony from veterinarians and veterinary technicians who have attended to the animals involved in a cruelty case are often the key to telling the story of an animal that has been injured or killed through abuse or neglect. Such testimony can address key issues raised in most cruelty cases, as outlined below. Veterinarians are among the most respected members of the community and their testimony as both direct and expert witnesses can be particularly compelling. Veterinary professionals can also provide a well-supported, objective community standard for what is considered reasonable and prudent care.

Major Roles of Veterinary Professionals in the Prosecution of Animal Cruelty Cases

- Documenting the physical condition of all animals associated with a cruelty case and documenting changes in their condition in response to care and treatment
- Commenting on reasonably prudent actions and standards of care that could have been taken to prevent disease, injury or death
- In the case of dead animals, determining the cause of death, sequence of injuries and timing of pre-mortem or post-mortem wounds
- Offering expert opinion to distinguish between death and injury resulting from human vs. non-human causes (eg, predation) or intentional vs. accidental injury
- Identifying and preserving physical evidence that may link the injuries to a particular suspect (eg, projectiles, ligatures, trace evidence).
- Offering opinions regarding the speed of unconsciousness or death, and degree of suffering to evaluate whether the death or killing was humane

Animal cruelty is increasingly viewed as a serious issue by professionals in law enforcement and mental health—as well as by the general public. Animals are part of the majority of American families, and their victimization is of concern to millions. The effective prosecution of animal abuse has many benefits. It can provide an early and timely response to those who are, or who are at risk of becoming, a threat to the safety of others. It can provide an added tool for the protection of those who are victims of family violence. It can provide an opportunity for prosecutors to develop new, strong and helpful allies in the protection of their communities. Finally, it can bring personal satisfaction in developing new skills and new understanding, and in helping build a truly compassionate society.

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ANIMAL HOARDING: RECOGNITION, RESPONSE, AND SENTENCING RECOMMENDATIONS

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Veterinarians may play several roles in the investigation, documentation, and resolution of an animal hoarding case. A veterinarian may be called upon to provide triage decisions at the scene of a hoarding situation, deciding which animals require immediate treatment or euthanasia for humane reasons and which may be treated later or impounded on the premises if possible. The veterinarian will play a central role in working with humane and law enforcement agents to document the condition of the animals, the nature and extent of illness and/or injury of each. He or she may be asked to outline long-term treatment protocols for the rehabilitation of animals that are malnourished, heavily infested with parasites, or otherwise severely ill, and may be called upon to identify the remains of dead animals found on the property and to offer opinions about cause of death.

The veterinarian is often asked to express an opinion regarding the duration of neglect, therefore particular attention should be paid to medical problems associated with chronic malnutrition, advanced progression of easily treated ailments, and prolonged exposure to unsanitary conditions. Such information is important in countering the explanation frequently offered by hoarders that the conditions are due to a recent lapse of care. The veterinarian may also be asked to state an opinion about how visible such problems would have been to a reasonable person, what steps could have been taken to prevent these problems, and the degree of pain or suffering experienced by the animals living in these conditions. And although a veterinarian is not an expert in human mental health, he or she may be asked to provide an opinion on sentencing or treatment options for hoarders since he or she can comment on the individual's ability to care for animals based on an understanding of the nature of the conditions of the animals who have been examined and treated.

Animal collecting is not, as it would seem at first glance, defined only by the number of animals one keeps. A person with an apparently manageable number of animals may exhibit symptoms characteristic of animal hoarding, while another is capable of providing adequate care for a much larger group of animals. The Hoarding of Animals Research Consortium defines an animal hoarder as "someone who accumulates a large number of animals; fails to provide minimal standards of nutrition, sanitation, and veterinary care; and fails to act on the deteriorating condition of the animals (including disease, starvation, and even death) or the environment (severe overcrowding, extremely unsanitary conditions) or the negative effect of the collection on their own health and well-being and on that of other household members."[8]

THE ANIMAL HOARDER

The stereotype of an animal hoarder is that of the "lonely little old cat lady," a woman who has turned to her cats for affection when the humans in her life have abandoned her. While animal hoarders do tend to be older females who live alone, an analysis of the psyche and motivations of those who hoard—whether they are hoarding animals or inanimate objects—paints a more comprehensive picture of the animal hoarder.

Hoarders of objects or animals typically are not distressed by their situation and are not motivated to change unless they are forced to either take action or risk losing their collection. Hoarders are extremely distressed if their items, no matter how useless they may seem, are taken from them. "It's like taking part of my body," explained one man who hoarded wood, nuts, bolts, nails, and broken, rusted electrical items. Their collection of items, although intended to give them control of their lives, often directly results in the loss of that control when the collection becomes so enormous or so hazardous as to require removal by others. While pathological collecting can be associated with a variety of mental disorders, including borderline personality disorder, schizophrenia and addiction, most experts consider many cases be a manifestation of obsessive-compulsive disorder. Only recently has it been realized that animal hoarding is yet another expression of hoarding behavior, involving not bits of wood and paper, but living animals.

The relationship between those who hoard animals and the animals themselves can vary. Most animal hoarders claim that their motivation for collecting animals is their love for them or their fear that no one else will care for them. Fear of euthanasia is also a common and distinct factor. Forty-three percent of hoarders are said to know all of their animals by name, whereas 33% know few, if any, by name.[8]

Many animal hoarders attempt to make caring for animals their vocation, professing themselves at some point in time to be animal shelters or rescue organizations. They may even gain legal nonprofit status from the IRS, accept donations from the public, and adopt out some of their animals. The HARC offers some guidelines for distinguishing between legitimate rescue groups and animal hoarders. Characteristics of a "rescue hoarder" may include:

- Unwilling to let visitors see the facilities where animals are kept
- Unwilling or unable to say how many animals are actually present
- Little effort made to adopt, and much effort focused on acquisition
- Continued acquisition in the face of declining care for existing animals
- Claims of being able to provide excellent lifetime care for animals with special needs (paralyzed,

feline leukemia positive, extreme aggression) without verifiable resources
- Number and staff and/or volunteers inconsistent with the number of animals allegedly being cared for
- Desire to receive animals at a remote location rather than on-site

Some cases of mass neglect of dogs or cats may be incorrectly identified as "hoarding" situations, when they are in fact simply "puppy mills" or poorly maintained breeding facilities. Usually such perpetrators have a history of selling or attempting to sell their animals, in contrast to true hoarders who rarely allow any animals to leave their care. However, this distinction is not always clear-cut. Some hoarding situations have involved breeders who initially bred their animals intentionally and sold them to the public or intended to sell them. Commercial animal breeding establishments are subject to regulation by the USDA pursuant to the Animal Welfare Act and must be licensed for commercial sales. Therefore, some animal hoarders have been USDA-licensed breeders. This distinction can be important in understanding the motivations of the individual responsible for the condition of the animals.

HOARDING VICTIMS

Although any species of animal can be involved, cats—perhaps because they are easily acquired and easily confined, and because they reproduce readily with minimal care—are the most common and most numerous victims, followed by dogs. Animals are acquired from various sources, primarily by unplanned breeding, but also as strays, from free-to-good-home ads, and from neighbors and other members of the general public who wish to relinquish their pets but do not want to take them to an animal shelter.

Depending on the severity and the duration of the situation, the animals may be in severely compromised condition or may be hardly affected. Veterinarians often find it surprising that animals taken from horrendous hoarding environments may have suffered fewer physical effects than would be expected. Other than some degree of emaciation, mild parasitic infestations, and viral diseases, some of these animals have no other telltale signs of their former plight. In such cases, the criminal charges or other actions must address the unfit environment in which the animals lived, and the inability of the caretaker to maintain a sanitary environment. One possible reason for the lack of effect of the hoarding environment on these animals is the adaptability of youth: The surviving animals are young and strong and have not yet succumbed to the stresses of the conditions in which they are living. In other situations, animals rescued from hoarding situations are in dire condition, infected with internal and external parasites, suffering severely from malnutrition and bacterial and viral infections. Complicating the situation may be the fact that these animals have not been socialized to contact with humans, and are difficult to capture, examine, treat, and provide care for.

More often than not, dead animals are found on the premises of animal hoarders[8] and criminal prosecution is much more likely in cases where dead animals have been found at the scene.[1] Hoarders may or may not recognize that these animals have died. Some animals are left to decay in the spot where they expired, whereas others are subjected to rituals which mark their death, such as being wrapped and placed in a freezer. At least one case involved a hoarder who also hid human cadavers on the premises.[10] Rarely are animal hoarders able to voluntarily part with one of their animals, living or dead. In death, as in life, they wish to maintain control over the animal. Some hoarders have been known to pick up and carry home "road kill" or other animal remains, complicating the investigative picture.

SPECIAL FORENSIC CONCERNS WHEN EXAMINING ANIMALS FROM HOARDING CASES

Effective resolution of an animal hoarding case, whether through prosecution, mental health evaluation, or negotiated surrender of some or all of the animals involved, requires a clear understanding of the nature of the abuse and neglect inflicted upon the animals. Investigators and veterinarians must document the condition of animals rescued from hoarding situations. This task is made more difficult by the large number of animals that may need to be assessed under adverse conditions. Although eventual charges may be based on a sampling of the animals recovered from the scene, it is important to document unique details for every animal victim, dead or alive.

Examination efforts will require specific attention to evidence that can be used to substantiate that the condition of the victims is the result of neglect of long-standing duration (weeks or months), was potentially obvious to a reasonably prudent person, was preventable through actions that would normally be undertaken by such a person, and was sufficient to cause extreme discomfort, pain, or suffering. The veterinarian needs to carefully document the recovery of the animals. This includes the animals' appetite on intake, weekly weight gain, and all the medical treatment needed. Photographic documentation of the animals' progress is critical. In addition, the initial mental status and behavior of the animal should be noted and if there are any changes over time.

Particular attention should be given to identifying evidence related to the following:

- Developmental conditions associated with long-term neglect and/or malnutrition. This might include bone disorders or deformities and other developmental abnormalities.
- Conditions associated with failure to provide routine care. This might include ingrown collars, heavily matted coats, and severely overgrown nails or hooves.
- Problems associated with inadequate monitoring of health, eg, large tumors or severely infected or abscessed wounds. Fights may be common in situations of heavy competition for limited food.

- Problems associated with advanced progression of preventable diseases, eg, enucleation of one or both eyes due to severe upper respiratory infection in cats.
- Conditions brought on by prolonged exposure to unsanitary bedding or flooring, such as urine scald or infection of the skin, feet, or toenails.
- Documentation of variety and extent of parasite loads. It is not uncommon to find nearly hairless dogs due to mange infestation in hoarder cases.
- Evidence of cannibalism and/or starvation and dehydration in any dead animals who are necropsied.
- In cases of large number of intact cats living in a confined area, evidence of forced matings may be seen. The barbs on the intact male cat's penis can cause vulva and vaginal abrasions from repeated, forced matings.
- Whenever there is intact animals living together there should be puppies or kittens. The lack thereof needs to be explained. Animals that are starving, under severe stress, or those that perceive the environment is unsafe may cannibalize their young.

THE ELUSIVENESS OF RESOLUTION

Although most prosecuted animal hoarding cases result in convictions or pleas,[1] these cases are notoriously difficult to resolve. Hoarders who are required to make restitution for veterinary costs rarely comply, although many agencies are able to recover such costs through public appeals. Those who are ordered to undergo psychological assessment and/or treatment also generally fail to comply. Many agencies have begun to promote a task force approach to respond to hoarding situations. Such groups involve representatives of all stakeholders in the community, including human health and social services, public health, zoning, code enforcement, and animal protection groups to bring a coordinated effort to these cases.

Successful resolution of these cases can be aided by careful veterinary and investigative documentation that can paint a clearer picture of what was allowed to happen to the animals involved and what level of care might be expected if animals are returned to the care of an animal hoarder.

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DOG FIGHTING CASE

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Although there are historical accounts of dogfights going back to the 1750s, widespread activity emerged after the Civil War, with professional pits proliferating in the 1860s, mainly in the Northeast. Many of the animals were brought from England and Ireland, where dog fighting had begun to flourish after bull-baiting and bear-baiting became illegal in the 1830s. Ironically, it was a common entertainment for police officers and firemen, and the "Police Gazette" served as a major source of information on dog fighting for many years. Although many laws were passed outlawing the activity, dog fighting continued to expand throughout the 20th century.

Throughout its history, the ASPCA has fought for stronger laws against all forms of animal cruelty. A 1981 report commissioned by the ASPCA entitled "Dog fighting in America: A National Overview," concluded that dog fighting was more widespread than the public or law enforcement imagined and that stronger laws at the state and federal level were needed.

WHO IS INVOLVED IN DOG FIGHTING?

Most law enforcement experts divide dogfight activity into three categories: street fighting, hobbyist fighting, and professional activity:

- **"Street"** fighters engage in dogfights that are informal, street corner, back alley and playground activities. Stripped of the rules and formality of the traditional pit fight, these are spontaneous events triggered by insults, turf invasions or the simple taunt, "My dog can kill yours." Many of these participants lack even a semblance of respect for the animals they fight, forcing them to train while wearing heavy chains to build stamina, and picking street fights in which they could get seriously hurt. Many of the dogs are bred to be a threat not only to other dogs, but to people as well—with tragic consequences.
- **"Hobbyist"** fighters are more organized, with one or more dogs participating in several organized fights a year as a sideline for both "entertainment" and to attempt to supplement income. They pay more attention to care and breeding of the dogs and are more likely to be traveling across state lines for events.
- **"Professional"** dog fighters often have large numbers of animals (often 50 or more) and earn money from breeding, selling and fighting dogs at a central location and on the road. They often pay particular attention to promoting established winning bloodlines and to long-term conditioning of animals. They regularly dispose of animals that are not successful fighters or breeders using a variety of methods, including shooting and blunt force trauma.

Unlike "professional" dog fighters of the past, both "professionals" and "hobbyists" of today may dispose of dogs that are too human-aggressive for the pit by selling them to "street" fighters or others who are simply looking for an aggressive dog—thus contributing to the dog bite problem.

HOW WIDESPREAD IS DOG FIGHTING IN AMERICA?

As with any other illegal underground activity, it is impossible to determine how many people may be involved in dog fighting. Estimates based on fight reports in underground dog fighting publications, and on animals entering shelters with evidence of fighting, suggest that the number of people involved in dog fighting in the US is in the tens of thousands.

While organized dog fighting activity seemed to decline in the 1990s, many law enforcement and animal control officials feel that it has rebounded in recent years. Street fighting has reportedly continued to grow as a significant component of urban crime. The Internet has also made it easier for dog fighters to rapidly exchange information about animals and fights.

Dog fighting has been reported in urban, suburban and rural settings in all regions of the country. Fighters were traditionally attracted to states with weaker penalties for dog fighting and animal cruelty, many in the South—but these laws have generally been made stronger throughout the country. As a result, this activity is no longer limited to any single area, but it is more likely to thrive wherever enforcement of these laws is weak.

WHAT TYPES OF PEOPLE ARE INVOLVED IN DOG FIGHTING?

Just as dog fighting cuts across many regions of the country, participants and spectators at dogfights are a diverse group. While some might typify dog fighting as a symptom of urban decay, not every dog fighter is economically disadvantaged. There are people who promote or participate in dog fighting from every community and background. Audiences contain lawyers, judges, and teachers drawn in by the excitement and thrill of the blood sport.

WHAT OTHER CRIMES ARE ASSOCIATED WITH DOG FIGHTING?

Many of the practices associated with the raising and training of fighting dogs can be prosecuted separately as animal abuse or neglect. In addition, dog fighting, by its very nature, involves illegal gambling. Dog fighters often face additional charges related to drug, alcohol and weapons violations as well as probation violations. Arguments over dog fights have also resulted in incidents that have led to charges of assault and even homicide. Other charges might include conspiracy, corruption of minors, money laundering, as well as several others.

WHAT DOGS ARE USED IN DOG FIGHTING?

Although there are many breeds of dogs used for fighting worldwide, the dog of choice for fighting in

America is the American Pit Bull Terrier. In addition, Boxers and Presa Canarios have also been used in this blood sport. Occasionally Doberman Pinschers or German Shepherds are reportedly used in street fights, or as "bait dogs" to train fighting dogs. "Professional" fighters and many "hobby" fighters seek dogs from known and proven fighting bloodlines. Other fighters unfortunately have a readily available supply of pit bulls of unknown origins and experience.

In the early days of dog fighting, the Bull Terrier was the dog of choice for this brutal blood sport, but it was replaced in the early 20th century by the American Pit Bull Terrier. One of the most popular dogs of the time, the American Pit Bull Terrier was noted for its strength, intelligence and devotion to its master. Responsible breeders who breed pit bulls as pets have generally selected **against** the high degree of aggression to other animals seen in fighting lines, while preserving the many desirable qualities of the breed. Dog fighters, on the other hand, have exploited these good qualities while placing the emphasis on "gameness," or the willingness to engage in prolonged combat.

HOW ARE FIGHTING DOGS RAISED AND TRAINED?

Fighting dogs must be kept isolated from other dogs, so they spend most of their lives on short heavy chains, often just out of reach of other dogs. They are usually poorly socialized to any other dogs and to most people. Many "professional" fighters invest much time and money in conditioning their animals. They are often given quality nutrition, basic veterinary care and exercised under controlled conditions where they will have limited contact with other dogs, such as on a treadmill or "jenny." The bodies or hides of cats or other small animals may be used to encourage the dog to run on such apparatus. However, more often than not, these bait animals are alive, and given to the fighting dog at the end of the exercise period to kill as a reward.

Fighting dogs used by all types of fighters usually have their ears cropped and tails docked close to their bodies. This serves two purposes. First, it limits the number of areas of the body that another dog might grab onto in a fight, and second, it makes it more difficult for other dogs to read the animal's mood and intentions through the normal body language cues most non-fighting dogs would use to reduce the need for aggressive encounters. Many fighters perform this cropping/docking themselves, using crude and inhumane techniques. This can lead them to face additional charges related to animal cruelty and/or the illegal practice of veterinary medicine.

The conditioning of fighting dogs may also make use of a variety of legal and illegal drugs, often including anabolic steroids to enhance muscle mass and encourage aggressiveness. Narcotic drugs may also be used to increase the dogs' aggression and mask pain during a fight. Dog fighters also often accumulate a large assortment of veterinary supplies for pain control and wound management, so that they can avoid trips to a veterinarian. Veterinarians in several states are specifically mandated to report suspected dogfight activity that comes to their attention through treating such animals.

Young animals are often trained or tested by allowing them to fight with other dogs while muzzled or leashed in well-controlled "rolls." Those that show little inclination to fight may be discarded or killed at an early age. Additional experienced is gained through fights with other dogs. Some fighters will use inexperienced "bait dogs" as sparring partners, often using stolen pets. "Professional" fighters claim to abhor this practice since it does not provide the animal with experience that is useful against another experienced fighting dog.

Although there are many other common techniques used in the training and testing of dogs, these methods vary widely among different fighters and may range from systematic to haphazard. "Street" fighters usually make little investment in conditioning their animals, relying on "quick fixes" to produce aggression. These might starvation, physical abuse, and use of stimulants or other drugs to excite the dogs.

WHAT GOES ON IN A DOG FIGHT?

As noted above, fights can take place in a variety of locations and at any time. They may be impromptu events in a back alley, or carefully planned and staged enterprises in a location specially designed and maintained for the purpose.

Usually the fight takes place in a pit that is between 14 and 20 feet square, with sides that may be plywood, hay bales, chain link or anything else that can contain the animals. The flooring may be dirt, wood, carpet or sawdust. The pit has "scratch lines" marked in opposite corners, where the dogs will face each other 12 to 14 feet apart.

In a more organized fight, the dogs will be weighed to make sure they are approximately the same weight. Handlers will often wash and examine the opponent's dog to remove any toxic substances that may have been placed on the fur in an attempt to harm the opposing dog.

At the start of the fight, the dogs are released from their corners and usually meet in the middle, seeking to get a hold on the opponent, often shaking and tearing to maximize damage. Handlers are not permitted to touch the dogs except when told to do so by the referee. This can happen if dogs become "fanged," with the tooth of one dog embedded in the skin of its opponent. Becoming "fanged" may require the use of a "breaking stick" (also called a "bite stick") to pry the animals apart.

If the action slows or if a dog turns away from his opponent without renewing his attack, the referee may call a "turn," and require that the dogs be returned to the corners and released after 20 to 30 seconds. If the dog that committed the "turn" fails to cross the pit and grip his opponent, the match is over and the other dog is the winner. A draw may occur if both dogs fail to "scratch" several times in succession, ie, repeatedly fail to cross the "scratch lines" and re-engage in the fight. This is generally a rare and unpopular end for those involved.

Fights can last several hours. Both animals may suffer injuries ranging from puncture wounds, lacerations and blood loss to dehydration, crushing injuries, and/or broken bones. Although fights are not technically fought to the death, many dogs succumb to their injuries. Losing dogs are often discarded, killed or left untreated, unless they have had a good history of past performance or come from valuable bloodlines. If the losing dog is perceived to be a particular embarrassment to the reputation or status of its owner, it may be executed in a particularly brutal fashion as part of the "entertainment."

WHAT ARE THE LAWS RELATING TO DOG FIGHTING?

Dog fighting is illegal in all 50 states and the District of Columbia, Puerto Rico and the Virgin Islands. As of 2007, dog fighting is a felony in all states except Idaho and Wyoming, where it is a misdemeanor. In most states, the possession of dogs for the purpose of fighting is also a felony offense. Being a spectator at a dogfight is currently a felony in 20 states, a misdemeanor in 28, and legal only in Georgia and Hawaii.

The federal Animal Welfare Act also prohibits the interstate transport of animals for the purposes of fighting. When federal animal fighting laws were initially enacted in 1976, no states made animal fighting a felony and federal law considered dog fighting activities to be a misdemeanor with a maximum sentence of one year. For this reason it was very rare that federal authorities were involved in the investigation or prosecution of dog fighting unless other crimes were associated with it, such as drug trafficking, alcohol or firearms violations, or financial crimes.

In 1999, Title 18, Section 48 was added to the US Code, making it a federal crime to "knowingly create, sell or possess a depiction of animal cruelty with the intention of placing that depiction in interstate or foreign commerce for commercial gain." The term "depiction of animal cruelty" means **any** visual or auditory depiction, including any photograph, motion-picture film, video recording, electronic image, or sound recording of conduct in which a living animal is intentionally maimed, mutilated, tortured, wounded, or killed—if such conduct is illegal under federal law or the law of the state in which the creation, sale, or possession takes place, **regardless of whether the maiming, mutilation, torture, wounding, or killing took place in the state**. This law was specifically enacted to address the proliferation of Internet sales of "crush videos" in which various small animals were shown being stepped on or otherwise killed. Despite its originally narrow focus, the law was used in 2005 to successfully prosecute a Virginia man charged with selling and mailing videotapes of fighting pit bulls.

In 2007, Congress passed the Animal Fighting Prohibition Enforcement Act with strong bipartisan support. The Act became law in May 2007, and provides for felony penalties for interstate commerce, import and export relating to commerce in fighting dogs, fighting cocks and cock fighting paraphernalia. Each violation can result in up to three years in jail and a $250,000 fine.

WHAT HAPPENS TO DOGS THAT ARE SEIZED FROM DOG FIGHT OPERATIONS? CAN THEY BE REHABILITATED?

Fighting dogs have been bred and trained to inflict injuries on other animals. They are difficult to house and care for. They are often relatively friendly to people, primarily adult males, since such people have been the only source of food and attention—but they can be unpredictable around people and any other animals. Confiscated fighting dogs are also at high risk of being stolen from shelters, foster care, or other placements and returned to the fight trade.

Concerns about liability, public safety and other risks mean that most animals seized from such operations are not adoptable, meaning they cannot be considered candidates for successful placement, and often have to be euthanized. Exceptions are sometimes made for puppies or other animals who show few signs of training or use in fighting, and who do not exhibit tendencies of significant aggression towards other animals or people. In some cases even animals that have been fought may be rehabilitated, but this can be a time-consuming process. However, such animals must be carefully evaluated by trained animal behavior professionals, such as Certified Applied Animal Behaviorists, and their placement must be monitored over the long term. Too often, animal control officers and animal welfare professionals are the only ones who show kindness and compassion to these animals, but it is too late to rehabilitate them—and then all they can do is give them a kind and peaceful end.

WHAT CAN COMMUNITIES DO TO COMBAT DOG FIGHTING?

The first step in combating dog fighting is for individuals to alert the authorities to any suspected or actual dog fighting activities in their area—identification of the problem is the first step to a solution.

In addition, the ASPCA recommends the formation of local or state task forces to address dog fighting. These groups should include members from all the major stakeholders in that community: law enforcement, prosecutors, animal control, animal welfare groups, veterinarians, public health officials, housing authorities, the neighborhood watch and others. The group should identify the nature of the problems in the area, the laws that could be applied to these problems, and the resources that are available. Dog fighting is most effectively addressed by a collaborative approach to this heinous crime.

The enforcement of animal cruelty laws begins with the individual. If you see something, please say something—notify your local police and/or humane law enforcement of any suspicious activities that suggest dog fighting is taking place in your community. For more tips on staying alert to signs of animal cruelty, click here.

MAKING THE CASE FOR NEGLECT: PROVING CAUSE, INTENT, TIMELINES

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DEFINITION OF NEGLECT

The legal definition of neglect varies by jurisdictions. It has traditionally been defined as a passive act or the lack of action that results in the neglect of an animal. It has also been viewed as an act without malice and therefore most jurisdictions treat neglect of an animal as a misdemeanor versus a felony. This is often the case even if the neglect results in the death of the animal. In severe or chronic neglect, there is a point on the continuum of the failure to act that the severity of the animal's condition and suffering has to have been obvious to the caregiver. At this point, when there is still failure to act it becomes a lack of action with malicious intent. This is when a neglect case can be potentially charged at a higher level as a felony. It is critical for the veterinarian to understand the nuances of the laws including local, state, and federal, in order to properly assist the investigator and prosecutor on the case.

Neglect can be anything the causes the animal to suffer. It can also be defined as anything that is inadequate or inappropriate for the animal taking into account environmental conditions, the species, gender, size, and age of the animal. Neglect can take many forms that negatively impact the animal's physical and mental well-being. These include the lack of or inappropriate shelter, food, water, bowls for food and water, tethering, preventative health care, medical treatment, embedded collars, and heavy chains.

The ordinances for Gwinnett County, Georgia are very detailed on their definitions of neglect and how animals should be taken care of:

SEC. 10-26. DEFINITIONS

Adequate food "means sufficient quantity of non-contaminated and nutritionally healthy sustenance that is appropriate to the species, breed, size, age and health of the animal, or at the direction of a licensed veterinarian, which is sufficient to prevent starvation, malnutrition, or risk to the animal's health. Garbage, spoiled, rancid, or contaminated food is not adequate food."

Adequate shelter "means a protective covering for an animal that is of adequate size and provides adequate protection to maintain the animal in a state of good health, and prevents pain, suffering, or significant risk to the animal's health. Adequate shelter shall consist of a completely enclosed structure with four (4) sides with a door opening, a constructed floor, and a roof. It should also be clean, dry and compatible with current weather conditions, in addition to age, size, species and condition of the animal. The structure should be of sufficient size to allow the animal to stand, turn around, lie down and go in and out of the structure comfortably. To be adequate, some type of bedding that is quick drying, such as hay or pine straw, must be provided to maintain comfortable temperatures within the structure during times when the ambient outside temperature is below freezing. In addition, the structure shall include a heavy plastic or rubber flap to cover the door and/or window openings during the months of November through March. From April through October, the structure shall either be shaded or moved out of direct sunlight. If the shelter is made of wood, it shall be raised at least two (2) inches off the ground to prevent seepage or rotting. Examples of inadequate shelter include, but are not limited to lean-tos, metal or plastic drums, boxes, abandoned vehicles, porches, decks, or material that does not provide sufficient protection from the elements."

Necessary veterinary care "means veterinary medical attention appropriate to the circumstances, whenever an animal is known or suspected to have suffered an injury, accidental or deliberate, or exhibits signs of disease process such as shock temperature fluctuations, tremors, swelling, broken bones, open wounds, inability to eat or drink, blistering, irregular or abnormal breathing, partial or total paralysis, abnormal discharge or bleeding, mage, or other signs of health problems."

Owner "means any person, firm, corporation, partnership, association, and/or other legal entity, who or which owns, possesses, harbors, keeps, feeds, maintains, or knowingly causes or knowingly permits an animal to be harbored or kept, or has an animal in his care, or who permits an animal to remain on or about his premises."

Sanitary conditions "means an animal living space, shelter, or exercise area that is not contaminated by health hazards, irritants, pollutants, items, or conditions that endanger or pose a risk to an animal's health."

SEC. 10-50. ANIMAL NEGLECT

(a) "Any animal or livestock owner or possessor who fails to provide adequate drink, adequate food, adequate space, adequate shelter, sanitary conditions, necessary veterinary care, and/or who causes unnecessary suffering of any animal or livestock shall be deemed in violation of this section." (b) "It shall be unlawful to leave animals unattended in a parked vehicle without proper ventilation to prevent the animal from suffering physical distress from heat exhaustion." (c) "Any animal control officer or other officer empowered to act by law may impound any animal found to be neglected, as defined by this section."

SEC. 10-29. RESTRAINT

(b) 4. "It shall be unlawful for the owner or possessor of any animal to restrain or anchor an animal by means of a tether, chain, cable, rope or cord, unless the tether or other restraint is being held by a competent person."

Another consideration in neglect is the mental well-being of the animal in the form of boredom, distress, and emotional maltreatment. Consideration must be given to the species, gender, breed, and age of the animal to determine what the mental needs of that particular animal are. Confinement and lack of stimulation leads to another form of suffering, boredom, which has physical and psychological impacts on the animal. The degree of boredom for an animal is most evident when one observes the behavior after the environment is changed to enriched conditions. Distress manifests as a result of how an animal copes with an unpleasant affect (physical or emotional) such as boredom, pain, thirst, hunger, loneliness, or fear. Evidence of unpleasant emotions in animals are fear, phobias, anxiety, separation anxiety, loneliness, boredom, frustration, anger, grief, helplessness, hopelessness and depression. Emotional maltreatment refers to the link between emotional states and physical health. Emotions can cause distress, anguish, and suffering. They can be associated with long term problems such as separation anxiety, decreased learning, depression, difficulty with social interactions, or even physical manifestations of illness.

PROVING CAUSE

When looking to the cause of neglect you are looking for the cause of the animal's failure to thrive. The veterinarian's job is not to determine the guilt or innocence or consider mitigating factors for the defendant. That is the investigator and prosecutor's responsibility. Often, there are multiple forms of neglect, multiple causes, and multiple animals affected. Disease is often present in neglect cases such as respiratory infections, intestinal parasites, and skin infections. In every animal cruelty case, a full laboratory work-up must be performed to determine the current health of the animal. This should include a CBC, chemistry panel, endocrine testing, fecal, urinalysis, heartworm, viral testing. Radiographs of the animal should be performed to look for occult injuries or problems. The veterinarian must then determine what was due to neglect and what may have been pre-existing and left untreated. In apparent starvation cases, it is critical to determine if there is an underlying health issue that is the cause. This often requires working with the investigator who interviewed the defendant, evaluating the crime scene findings, and reviewing any previous medical records. Sometimes the test results can indicate the chronicity of the problem, such as monocytosis. Any deceased animals on the scene should be properly collected or exhumed for examination. Depending on the degree of decomposition, a bone marrow fat analysis can be conducted to determine if the animal died of end-stage starvation. The skeletal remains should be examined by a specialist for identification and cause of death determination.

At the scene, photographs and video should be taken of the environment and of the animal(s). The crime scene must be meticulously examined for all evidence of neglect. Special attention should be paid to the food and water available to the animal as well as the stock of food on the premises. The expiration dates on any food labels should be recorded. Any medication found should be recorded including the veterinary hospital, prescribing doctor, date of prescription, animal prescribed for, expiration date, instructions, if stored per label instructions, and amount used. Factors such as over-crowding and extreme environmental conditions should be documented.

The cause of neglect is often due to a multiple of factors and problems. It is important to list every problem with the animal, environment, and husbandry in the report. Whenever possible, each item should be identified as primary and secondary problems. It is also crucial to include in the report what steps could have been taken to prevent the suffering of the animal, especially when they were simple and low-cost. Every judge and jury has their own level of experience with animals and their own minimum standards for the care of an animal. One never knows what will stick out as significant to the judge or jury so it is imperative to include every finding in the report and testimony.

There are psychological factors in some neglect cases which are a consideration of where and how to look for evidence as well as for the prosecution. Munchausen syndrome by proxy may be an issue of there is a history of repetitive unusual medical problems for the pets in the family. Animal hoarders are animal abusers whose actions are the results of a complex and poorly understood mental condition. Animal hoarding is defined as someone who has accumulated a large number of animals that overwhelmed their ability to provide a minimum of care including adequate nutrition, sanitary conditions, and veterinary care. Animal hoarding is about the need to accumulate and control animals which supersedes the needs of the animals. In addition, animal hoarders usually hoard other items such as newspapers, magazines, clothes, videos and so on. Often, hoarding is precipitated by a personal loss or some other major negative event in their life. There are some large-scale animal cases that are not truly hoarders but instead are cases of sadism and/or serial animal killers. Each case must be examined looking at the totality of the problem to determine the proper action by investigators and prosecutors.

PROVING INTENT

As discussed earlier, neglect is traditionally viewed as a passive act without malicious intent. Depending on the circumstances, the case may have elements of malicious intent – where the defendant acted or failed to act with malicious intent. There is something in the legal system known as the "Reasonable Person Standard." What this refers to is 'the result a reasonable person would expect with the given set of actions or inactions'. This is where the veterinarian's expertise comes into play in the case. A veterinarian can testify as to the condition of the animal and give an estimation of the time the animal has been in such condition. This is done by establishing timelines.

ESTABLISHING TIMELINES

There are several ways to establish timelines on neglect cases. Sometimes one may only be able to say several weeks or months. At the scene, the vegetation can give a clue to the chronicity of the conditions. The lack of vegetation indicates the animal has been in that area for awhile. The high growth of weeds indicates nothing has been on that area for period of time. The lack of feces in the area of the animal indicates either the area was cleaned up, the animal has not been ingesting food in order to produce feces, or exhibiting copraphagy. The high buildup of feces can be used to give an estimate of time for the conditions. Using a minimum of one bowel movement a day, one can develop a rough timeline. The build up of dirt and debris around a gate opening indicate the lack of use for an extended period. The utility records can be obtained to determine usage. The dating on mail can also help establish the presence of the defendant. Any veterinary medications and records can help determine length of ownership.

Wounds that have granulation tissue can be biopsied and the granulation tissue measured to determine the estimated time for healing. The granulation bed forms 3 to 5 days after injury. It forms at the edge of the wound at a rate of 0.4 to 1 mm/day. In general, granulation tissue grows at a rate of 1mm/day and slows as the lesion ages to 1 cm/month.

It is not uncommon to find maggots infesting the wounds of an animal if in the appropriate climate when flies are still active. This is called myiasis. The maggots can be used to give an estimate for the length of time for the wound. The maggots are attracted to the smells associated with decay and infection. They will lay eggs on live animals with necrotic, bloody, infected wounds. These maggots should be collected, along with appropriate weather data, and submitted to a forensic entomologist.

One cannot give an exact time frame for an animal to have lost a certain amount of weight. It depends on the life stage of the animal, their initial body condition score, the amount of food fed, quality of food, and frequency of feeding. What veterinarians can say is the minimum time frame based on their clinical experience. An animal does not reach the lowest body condition score due to starvation in a matter of two weeks. All veterinarians have seen animals in private practice that have not eaten for 2 weeks. So, one can say it has to have been several weeks, greater than 2. Remember, an animal will succumb to dehydration before starvation. The exam findings in conjunction with crime scene findings and interview results by investigators should help to establish more accurate timelines.

MAKING THE CASE FOR NON-ACCIDENTAL INJURY: PROVING CAUSE, SEQUENCE OF EVENTS, & TIME OF DEATH

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PROVING CAUSE OF NON-ACCIDENTAL INJURY

There are many different types of non-accidental injuries. They include penetrating injuries, non-penetrating injuries, burns, gunshot wounds, asphyxia, drowning, poisoning, ritualistic crime, sexual assault, and animal fighting injuries. There are several considerations to first determine if the injury is a result of accidental versus non-accidental causes. The veterinarian must draw on their own experience with known accidental injuries and compare those findings to the evaluation. Another source of information is emergency veterinarians who have a wealth of knowledge and experience with trauma though some of their cases may have been undetected abuse. The information provided by the caregiver and/or the investigator is critical to properly evaluate a possible case of cruelty, whether the animal is alive or deceased. A necropsy should never be performed without investigation findings and crime scene information including photographs of the scene. The environment and husbandry for the animal directly affects the health of the animal and must be analyzed along with physical exam findings. Animal cruelty should be suspected in every case where the history, crime scene findings, and environmental conditions do not support the exam findings. Aberrant findings should not be disregarded for they are often the key piece of evidence that the injuries sustained are non-accidental.

The causes of non-accidental injury are limited only by the perpetrator's imagination. To try and surmise the cause and/or weapons used, one must first examine the body for injury patterns. These will give the greatest clues as to the cause of injury. When weapons are used, either in penetrating or non-penetrating injuries, a corresponding weapon pattern may be found on the body. These can be in the form of distinct bruising, skin injury, or damage to bones. If a significant time period has elapsed since the injury occurred, the bruising may spread obscuring any distinct weapon patterns. The skin injury may present as patterned hair loss due to crushing forces, abrasions, or full-thickness defects. A rubber cast should be made of any weapon pattern on bones or full-thickness skin defects. Mikrosil is used for rubber casting and is available from most criminal supply sources. Mikrosil comes in different colors and brown is the preferred color for tool mark examiners. The rubber cast is then used to help identify what type of weapon may have been used or confirm any suspected weapon. In some cases, the weapon may have left residue, such as oil or wood fragments, on the fur, skin, wound edges, or embedded inside the wound. All areas should be carefully examined with a magnifier to detect any evidence and collected appropriately.

Bone fractures are caused by certain physical forces. Each fracture must be evaluated considering the type of force required to produce that particular type of fracture. In addition, the type of bone, the age of the animal, growth plate closures, the size of the animal, the density of the bone, and the location of the fracture are all factors in determining accidental versus non-accidental causes. A transverse fracture is caused by a perpendicular blow to the bone. Rotational forces to a bone will cause spiral fractures. An adult dog that presents with a transverse fracture of the humerus; the history is the dog jumped down off a table to the ground, injuring the leg. The history does not match the type of fracture produced, the age of the dog, the location of the fracture, and the density of the bone. If the history were true, the dog should have a spiral fracture of the lower leg, not a transverse fracture of the humerus which is caused by a direct blow. Weapons may cause depression fractures or, if a wide object is used, there may be a several fractures over the area hit. There may also be corresponding fractures on the opposite side of the body if the blow to one side of the animal caused the body to impact a hard surface on the opposite side with enough force to cause a fracture. This is most commonly seen on the skull when the zygomatic arch on the opposite side impacts a hard surface due to a blow to the head. Organized dog fighting can produce punctures in bones, depression fractures, and gouges to bones. Tail injuries are common in animal cruelty cases. The tail may be used to hold the animal up, either by hand or ligature. There may be evidence of a ligature with trace evidence on the fur, ligature patterns on the skin, skin abrasions, or degloving injuries. There may be fractures or dislocations of the tail indicating crushing or pulling forces were used. The rule-outs for accidental trauma to the tail are getting caught in a door or stepping on the tail. These particular injuries should be located at the distal aspect of the tail.

With every animal cruelty case, one must consider the animal suffered blunt force trauma in addition to any other injuries. Contusions are very hard to see on the skin surface of animals unless there is light colored skin and the fur is parted all over the body to inspect for discoloration. It can take hours for bruising to show up on a live animal so re-inspection of the body should be done every few hours. In deceased animals, the skin should be reflected all over the body to reveal subcutaneous hemorrhage. Sometimes the hemorrhage is in the deeper muscle next to the bone, such as the rib cage, and does not extend to the subcutaneous layers especially if the survival period was very short after the injury. Careful dissection of the muscle layers can reveal the deeper evidence of trauma. The size and shape of the contusions can help determine what was used to cause the injury. There may be a denser area of hemorrhage with seepage into the surrounding tissues. It is the denser area that provides the clues to the cause. Petechiae may be seen on the pinnae and horizontal ear canal with blunt force trauma to the head. The petechia in the ear canal is a unique finding in dogs and cats due to the shape of their ear canal. Frank hemorrhage may be seen inside the ear due to a ruptured tympanic membrane. The common rule-out for any hemorrhage is clotting disorders which have a wide variety of causes so a full workup should be conducted.

Burns may be caused by a variety of methods including chemicals, thermal, scalding, and fire. The appearance of the burn provides several clues as to the cause of the burn. Burns are usually a patterned injury that reflects the cause of the injury. It is the proper interpretation of the burn patterns can reveal the exact nature of events which may support or refute the history. A determination of where the burn started on the body may be made when there are more severe burns confluent with more superficial burns. Splash or spill burns have trickle-like areas that are usually more superficial than where the liquid first contacted the body. A burn pattern that is evenly distributed with the same degree of injury is indicative of an even rate of burn.

For all trauma cases, the most common rule-outs are motor vehicle accidents (MVA) and dog attack. With MVA injuries, there should be certain findings that are supportive of this type of cause. There should be dirt and debris on the fur; skin abrasions from the animal sliding on pavement or dirt; the abrasions should be lateral on the down side and medial on the opposite side; and frayed nails (most commonly found with cats). These findings are in addition to any injuries sustained from being hit, rolled under, or run over by a car such as blunt force trauma and fractures. In dog attacks, there should also be supportive findings of the cause. There is often dirt and debris in the mouth where the animal was dragged and shake on the ground; head and oral trauma from being shaken by the neck or grabbed by the head; saliva on the fur which causes spiking of the fur; fur caught in the nails where the victim fought the attacker (especially cats); punctures of the skin which may be triangular or elliptical; and abdominal organ lacerations from compression and shaking with or without associated skin punctures.

Detailed photo documentation should be made of all injuries including a photo scale next to the affected area. Detailed measurements of each injury should be made including a measurement from a landmark on the body. For multiple injuries, a letter or number system should be used to identify each injury. There should be at least one photograph of each injury and piece of evidence that will accurately portray what happened and can be blown up for courtroom use. It is helpful for investigators and the prosecutor to use a diagram of an animal or anatomical area to mark the injured areas.

PROVING SEQUENCE OF EVENTS

It is important to try and determine the sequence of injuries which re-creates the crime scene events. The veterinarian's knowledge of animal behavior, clinical experience, and common sense must be used to evaluate injuries. There are several considerations to make this determination depending on the type of injury. In deceased victims, the first thing to determine is the fatal injury and then back track from there. For contusions and areas of hemorrhage, one must remember that hemorrhage requires a beating heart. In multiple stab wounds, there may be little to no hemorrhage around an injury that was made when or after the heart stopped beating. But, if there is minimal blood supply to the area then it could account for the minimal amount of hemorrhage.

With multiple fractures or injuries, a diagram can help in the evaluation of the number of blows and determining sequence of events. With multiple fractures of the skull, one blow may cause concentric or radiating fractures. Evaluation of where these lines stop and start can help determine the number and type of impacts. Consideration must be given to the impact each injury would have had to the animal. This includes how the injury would have compromised the animal such as severe pain, the ability to move, vocalize, or fight back. In addition, the veterinarian must consider what the animal's response would have been to each injury. This is critical in courtroom where the veterinarian must testify about the expected reaction and vocalization to each event/injury as part of their expert witness testimony.

PROVING TIME OF DEATH

Proving time of death is usually an estimate at best. It requires taking into account several exam findings in addition to eye witness statements. Rigor mortis, algor mortis, and gastric emptying time are all variable depending on the events prior to death and the environmental conditions. The most accurate time of death can be provided using insect evidence. Maggots can aid in determining TOD, location of death and provide DNA and toxicology evidence. Maggots can help determine the time of death by providing the post mortem interval. Flies lay eggs during certain environmental conditions, at certain times of day after an animal has died depending on the species of fly. These eggs then hatch into maggots based on environmental conditions. The larvae develop at a certain rate, depending on the species and environmental conditions, and can be aged by a forensic entomologist. Blow flies are attracted to the body postmortem so by dating the time of colonization (laying of eggs), the time of death can be estimated. It is important to note that in some cases, maggots may be found on live animals, known as myasis. This is usually due to fecal soiling or wound necrosis present on the animal that attracted the flies. In this case, the time estimate will be for the time of trauma. Other insects are forensically important such as beetles which feed at different times post mortem.

A sample of all insects, pupae and pupa casings on the body should be collected noting the location on the body they were found. If there is a mass of maggots, then a temperature of the mass must be taken by inserting a thermometer in the center. The mass of maggots generates heat affecting their rate of development and affecting the entomologist's analysis. In some cases there may be pupae casings present indicating the fly has gone through at least one life cycle and these should be collected. If maggots are present then it is important to get a sample of the adult flies to assist maggot species identification. One should also get a sample of any beetles if present which appear on deceased bodies at certain time intervals after death. Maggot samples should be collected and shipped for testing, taking care to get the largest larvae.

Forensic entomology analysis is dependent on the ambient temperature readings. Weather data for the past 2 to 3 weeks as well as temperature of where the body had been held prior to examination is needed for accurate analysis. When the body is moved from the scene temperature of the transport vehicle and the time of transport must be recorded. If the body is held in a cooler prior to maggot sample collection, the temperature and time in the cooler must also be recorded. The entomologist needs certain information in addition to the weather data. They need photographs of the animal and the environment it was found in. They need to know if there were any unhatched eggs on the body and the location. They need to know the position of the body when found at the scene – sternal, lateral, curled, anything covering the body, and if the body was in direct sunlight or under shade taking special note of the head and perineal area. It is also helpful to provide them with any information regarding the crime scene and the presumptive cause of death.

Every effort should be made to get a sample of live flies at the scene where maggots or maggot eggs are present for species identification. Blow fly egg masses should first be photographed and their location documented. Using forceps, break a small piece of egg mass off approximately the size of a dime, taking care to collect from the center as the eggs at the edge may be desiccated and no longer viable. Each egg mass collected from each location on the body should be kept separate. The mass collected should be broken in half and one half placed in 75% ethyl alcohol. The other half should be placed in a larval-rearing pouch. These pouches are made taking a piece of aluminum foil and folding it to create a three-dimensional rectangular pouch, crimping the corners together. A small piece of beef or pork liver should be placed inside as a feeding substrate should the larvae hatch. The top should be crimped together sealing the sample. This pouch should then be placed inside a plastic container for shipment with approximately one inch of soil or vermiculite in the bottom and small air-holes punched into the plastic top. This substrate absorbs any fluids that leak from the pouch and, for late stage larval samples, provides a burrowing substrate.

Two labels should be created for the larval feeding pouch with the date and time, case number, location of the sample collected, and the sample number. These should be filled out in pencil to avoid any destruction of the writing. There should always be a double labeling system used where one label is placed inside the plastic container and the other affixed to the outside of the container. For all samples, note the time they were placed in the container and when they were shipped.

When collecting maggots for analysis, you are looking for the oldest (largest) larvae because they are the ones that first hatched and in turn were the first eggs laid. At first, the body and the surrounding area should be examined for prepupal maggots (post-feeding). These will most likely be found off the body but may be found in the fur, carpet, the first 3 to 5 cm of soil, or up to 50 meters from the body. If none are found then samples of the largest instar larvae should be collected, noting their location on the body. Temperature recordings and time of collection should be documented as described above.

A sample of the collected maggots should be preserved at the scene. Place a sample of the largest maggots and some of the next size down into hot or boiling water for five minutes to kill and blanch them documenting the time of blanching. They should then be transferred to a vial of 70% to 85% isopropyl alcohol. They may be placed in 70% to 85% isopropyl alcohol at the scene if hot water is not available for blanching. The vial should be double-labeled as described with egg masses, with one label in the liquid and another affixed to the outside. Another live sample of the maggots should be preserved for examination using the larval-rearing pouches. Do not put too many maggots in the pouch because they need air and too many could cause the majority or all of them to die.

The migratory larvae and puparia may be found usually within 20 to 30 feet of the body, depending on the species. They may be found under surface debris, in the top few inches of soft soil, vegetation, under rocks, or on tree trunks. The presence of the empty pupa cases indicates that a complete blow fly life cycle has taken place on the body and indicates a minimum elapsed time since death. These casings are often mistaken for rat droppings. They may be found in the same areas as the prepupal maggots and the pupae. Newly emerged adult flies should be collected in dry vials and a description of their appearance noted, as it will change by the time it reaches the forensic entomologist. As time goes on, there is sequential colonization of the remains by other insects. Analyses of these later appearing insects can help with the estimate of the postmortem interval.

HISTIOCYTIC ULCERATIVE COLITIS – WHAT'S NEW?

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CLINICAL AND HISTOPATHOLOGIC FEATURES OF CANINE HISTIOCYTIC ULCERATIVE COLITIS

Histiocytic ulcerative colitis (HUC) is a form of inflammatory bowel disease which occurs most frequently in young Boxer dogs. It was first described 30 years ago and has since then been reported to occur in many countries, including the United States, Australia, Japan, and in Europe, particularly in the United Kingdom.[9] In addition to Boxers, HUC has also been reported to occur infrequently in other breeds, such as Mastiffs, Alaskan Malamutes, French Bulldogs, English Bulldogs, and even in one cat. The onset of disease is predominantly in dogs younger than 2 years of age. The clinical signs are those of severe chronic large intestinal inflammation and comprise diarrhea, hematochezia, increased frequency of defecation, tenesmus, and excessive mucus in the feces. Weight loss and inappetence can also be seen in severe cases.

Endoscopic findings demonstrate sites of severe colonic hemorrhage and ulcerations interspersed with stretches of normal appearing mucosa. Histologically, early lesions can present with a mixed inflammatory infiltrate in the lamina propria, which are subjacent to degenerative epithelium. With more extensive lesions and chronic disease, the ulcerations become more visible on histology with severe infiltration of the lamina propria and the submucosal regions with neutrophils, macrophages, lymphocytes, plasma cells, and mast cells. There is also usually massive loss of the epithelial surface in biopsies from lesions and loss of goblet cells in the entire colon. The pathognomonic histologic lesion, however, is the accumulation of large macrophages which stain strongly positive with periodic acid–Schiff (PAS) in their cytoplasm. This is still the best way to diagnose HUC with certainty.

Immunohistochemical studies have shown that HUC lesions are characterized by an increased number of L1-positive cells, as well as MHC class II–positive cells, CD3-positive cells, and IgG-positive plasma cells. L1 is a cytosolic calcium-binding protein whose function has not been described in detail in the dog; however, in humans it is expressed on macrophages and neutrophils in an early stage in their differentiation and is lost when macrophages migrate into tissues and mature. It is possible that in canine HUC, recently emigrated blood monocytes progressively differentiate into tissue macrophages, and become eventually expanded with PAS-positive material, while L1 expression is down-regulated. MHC class II molecules are present on all PAS-positive macrophages in HUC lesions, and it is therefore not surprising to find an increased MHCII expression in HUC. T-cell numbers were also shown to be increased in HUC, which concurs with finding an increased number of CD3-positive cells in other forms of canine IBD, particularly lymphoplasmacytic IBD.

TREATMENT OF HUC

Unfortunately, the prognosis for HUC has been guarded to poor until just recently. Management of HUC consisted of various combinations of dietary management (eg, increasing fiber content in the diet and specific elimination diets), and anti-inflammatory or immunosuppressive treatment with sulfasalazine, prednisolone, and azathioprine. However, these strategies usually failed to improve the clinical signs in affected animals, and most animals had to be euthanized because of refractoriness to treatment.

Two recent reports have now sparked hope in treating the disease, as a total of 12 cases have been reported which have shown dramatic response to treatment with enrofloxacin (5 mg/kg PO once daily) or a combination protocol with enrofloxacin, amoxicillin (20 mg/kg PO twice daily) and metronidazole (10–15 mg/kg PO twice daily). These findings are intriguing, as very early reports describing the disease almost 30 years ago have also occasionally described a good response to treatment to antibiotics, namely chloramphenicol and tetracycline. The response to treatment with enrofloxacin in the more recent reports was dramatic, with all dogs responding within 3 to 12 days of starting treatment. It is particularly encouraging that several dogs were reportedly disease-free when the drug had been discontinued after finishing a course of 4 to 6 weeks of antibiotic treatment with enrofloxacin. This implies a possibility of curing the disease in certain cases, even though follow-up times of more than 21 months have not been reported so far and it is possible that some dogs need treatment with enrofloxacin for much longer than 6 weeks or possibly even life-long treatment. In 5 of the reported cases, biopsies were repeated after finishing the course of antibiotic treatment at the time when the dogs were in clinical remission. In all of these 5 dogs, a dramatic improvement in the histologic lesions was demonstrated, with disappearance of PAS-positive macrophages in three cases and a marked reduction in the number of macrophages in the other two cases.

INVESTIGATIONS INTO THE PATHOGENESIS OF HUC

The mechanisms involved in the pathogenesis of HUC in dogs have been debated for decades. The recent success with antibiotic treatment in canine HUC obviously raises the question whether HUC could be caused by an infectious organism. It is not the first time that this hypothesis has been investigated. The role played by the PAS-positive macrophages is intriguing, as PAS stains intracellular phagocytosed material in the macrophages, and early electron microscopic studies have demonstrated so-called "residual bodies," which resemble bacteria-like organisms in PAS-positive staining macrophages. These particles contained parallel pairs of membranes, and electron-dense particles ranging in size from 100-500 nm which could have represented bacterial cell membranes. Therefore, specific infectious agents, such as Mycobacteria, Mycoplasma, Chlamydia, and Rickettsiae have all been proposed to play a role in the pathogenesis of the disease. However, attempts to reproduce the disease by infecting dogs with *Mycoplasma* spp. have failed.

Some reports have compared Whipple's disease in humans with canine HUC. Whipple's disease in humans is caused by *Tropheryma whipplei* and mainly affects the small intestine as opposed to the colon in canine HUC; however, histologically, there is a striking resemblance. In both diseases, severe granulomatous inflammation and distortion of the lamina propria of the bowel can be seen. The causative organism in Whipple's disease is susceptible to a variety of antibiotics, such as penicillin, chloramphenicol, and tetracycline, but seems to be resistant to enrofloxacins. *Tropheryma whipplei* has so far not been identified in dogs with HUC, but the overwhelming treatment success with enrofloxacin seems to makes this organism less plausible as a possible causative agent for HUC.

In a recent publication investigating the possibility of an infectious cause for canine HUC, intiriguingly large numbers of coccobacilli were found by fluorescent in situ hybridization in the colonic mucosa of Boxers affected with HUC, as opposed to histologically normal tissues and in the mucosa of dogs with other types of colitis. Further studies by culture, cloning, and sequencing of the flora in the colon of Boxers with HUC identified the bacteria to be E. coli. The bacteria could be identified by electron microscopy and localized to the intracellular compartment in PAS-positive macrophages in HUC lesions. This finding is exciting, particularly because further classification of the virulence genes and biological behavior of these bacteria in co-culture with epithelial cells and macrophages revealed specific adhesive and invasive properties. The *E. coli* strains associated with HUC were shown to have a similar phenotype and adhesive and invasive behavior resembling *E. coli* isolates which have recently been associated with Crohn's disease in people. In several studies, a particular strain of *E. coli*, so-called *E. coli* LF82, could be demonstrated in biopsies of 20% to 35% of ileal lesions in Crohn's disease, but never in healthy controls or other colitic diseases.

Why is this so important with regards to canine HUC? Crohn's disease is a condition in humans that affects primarily the mucosa and submucosa of the ileum and colon. It resembles canine HUC in its histologic appearance, as granulomas are the main feature of the disease. Just as in canine HUC, some cases of Crohn's disease seem to be susceptible to treatment with antibiotics. The *E. coli* strain LF82 which has increasingly been associated with Crohn's disease is unusual in the sense that these bacteria will not cause any intestinal pathology in most people, insofar as they actually represent "commensals" in the microflora of most humans. This finding fits nicely in the hypothesis that genetics play another big role in the pathogenesis of Crohn's disease, and possibly, also in canine HUC. There is increasing evidence that in Crohn's disease, an overly aggressive immune response to luminal commensal bacteria, specifically *E. coli* LF82, is implicated in the development of the disease. What this means is that, in genetically susceptible individuals, specific strains of *E. coli* which will not cause disease in other individuals, can lead to the development of severe inflammation in people susceptible to developing Crohns' disease.

There has also been recent progress in identifying which specific genetic defects are responsible for such a hyper-responsiveness of the gut immune system towards commensal bacteria from the microflora. Genetic defects in certain receptors of the innate immunity have been identified in people with IBD. These receptors are important for the interaction of the innate immune system in the intestinal mucosa with the microflora in the intestinal lumen. The gut epithelium detects the presence of both commensal and pathogenic bacteria via pattern recognition receptors (PRP). The main classes of PRR in which mutations have been found in people with IBD are Toll-like receptors (TLRs, specifically TLR4) and nucleotide binding oligomerization domain-like receptors (NODs, specifically NOD2). These receptors recognize specific molecules termed *pathogen-associated molecular patterns* (PAMPs), which are conserved molecules found on bacteria and other infectious agents. Recognition of PAMPs by TLRs is a crucial part of the innate immune response to invading bacteria in the gut and initiates a complex intracellular signaling pathway culminating in the activation of the transcription factor NF-κB. This results in the transcription and secretion of a variety of pro- and anti-inflammatory cytokines and chemokines from the cell bearing the TLR. This response attempts to clear offending pathogens, yet in the normal case scenario remains inert towards commensal organisms from the intestinal lumen.

The inflammatory response, which is normally only seen as a reaction towards pathogenic bacteria breaching the intestinal barrier, is similar to what is seen in the mucosa of people affected with Crohn's disease and dogs affected with HUC. It is therefore possible that similar defects in pattern-recognition receptors as found in people with IBD could be found in dogs with HUC. A genetic predisposition seems to be one of the obvious mechanisms involved, as most cases described are young Boxer dogs, and in the first report of the disease in 1965, most of the affected dogs could be traced back to a single ancestor. Whether Boxers with HUC carry mutations in pattern-recognition receptors such as TLRs or NODs remains to be determined; however, it seems likely that a defect in the innate immunity renders dogs with HUC more susceptible to specific infections, such as *E. coli* strains which do dot cause disease in normal animals.

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CHRONIC PANCREATITIS IN CANINE IBD

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Inflammatory bowel disease–associated chronic pancreatitis (IBD-CP) is well known as a clinical entity in people, as episodes of pancreatitis occur in many human patients during the course of inflammatory bowel disease. Although the etiology of chronic pancreatitis in people with IBD is unknown, the clinical, morphologic, and histologic features are reminiscent of autoimmune pancreatitis. Autoimmune pancreatitis is commonly subclinical and is the only form of chronic pancreatitis in people that is completely responsive to steroids. Clinical symptoms of IBD-CP are found in approximately 2% of human patients but the actual frequency of the disease could be much higher since according to several studies hyperamylasemia and exocrine pancreatic insufficiency are found in 6% to 16% and 21% to 80% of patients, respectively, whereas histologic changes are observed in 38% to 53% of post-mortem pathological examinations. Therefore, it appears that IBD-CP could mainly be a clinically silent disease.

IBD-CP has so far not been reported in dogs. Chronic pancreatitis as a separate disease entity has been under-recognized in dogs, but several studies have shown that it may be more common than perceived. Diagnosing pancreatitis, especially chronic pancreatitis, in dogs is very challenging. Clinical signs are nonspecific and can easily be confused with those of the IBD itself. Elevated amylase and lipase can be affected by other nonpancreatic conditions and have relatively low specificity and sensitivity for pancreatitis. Abdominal radiographs are subjective, rely on the quality of the radiograph and the experience of the reader, and are nonspecific for canine pancreatitis. The sensitivity of abdominal ultrasound for diagnosing pancreatitis is highly operator dependent and reported to be up to 68% in dogs. Although pancreatic biopsy was once considered to be the gold standard, we know from various studies that the site of inflammation can be missed.

So far, canine pancreatic lipase immunoreactivity (cPLI) is considered to be the best test for the diagnosis of canine pancreatitis. We recently performed a retrospective study at the University of London looking at canine IBD cases with elevated cPLI values. The aims of the study were to determine whether IBD-CP exists in dogs and if so to determine the prevalence and characteristics of canine IBD-CP.

MATERIALS AND METHODS

Forty-seven canine patients with confirmed IBD on histopathology were prospectively enrolled into the study. Serum was stored from these dogs and sent away for cPLI measurement (performed at the Texas GI Laboratory). According to their cPLI results the dogs were retrospectively separated into two groups; those above the laboratory reference range of 200 µg/L were designated as IBD with chronic pancreatitis (IBD-CP) and those with results less than 200 µg/L as IBD-without associated chronic pancreatitis (IBD-NCP).

The IBD workup in all cases was retrospectively evaluated and comparisons were made of the following parameters between the two groups: clinical signs, age, serum lipase and amylase activities, serum albumin and cobalamin concentrations, abdominal ultrasound findings, histopathologic findings on intestinal biopsies, management of IBD, and clinical outcome.

RESULTS

No significant differences were found in clinical activity score (*P*=0.67), serum amylase activity (*P*=0.058), serum cobalamin concentration (*P*=0.61), serum albumin concentration (*P*=0.052), abdominal ultrasound scores (*P*=0.23) and histopathology scores for IBD (*P*=0.74). There was also no significant difference in the frequency of steroid treatment between the two groups (*P*=0.13). Dogs with IBD-CP were found to be significantly older and had a higher serum lipase concentration than dogs with IBD-NCP (*P*=0.001, *P*=0.001, respectively). Moreover, dogs with IBD-CP had a higher risk of a poor follow-up score (*P*=0.02) and were significantly more likely to be euthanized at follow-up (*P*=0.02).

CLINICAL SIGNIFICANCE

In this study, 15 out of 41 dogs with confirmed inflammatory bowel disease had elevated serum cPLI results supporting a diagnosis of IBD-CP. In people, abdominal pain is the cardinal sign for pancreatitis and when present clinical pancreatitis is diagnosed. If taking abdominal pain as a criterion to diagnose clinical pancreatitis, then 2% of our study population were clinical for pancreatitis and 33% had subclinical pancreatitis based on the absence of clinical signs attributable to pancreatitis. This mirrors the findings in IBD-CP and autoimmune pancreatitis in people.

Dogs with IBD-CP had a significantly poorer outcome score and were significantly more likely to be euthanized at follow-up. This was probably because the second diagnosis of chronic pancreatitis was missed in the IBD patients as cPLI was only determined retrospectively for the purpose of this study. Appropriate treatment for chronic pancreatitis such as low-fat diet or pancreatic enzyme replacement was not attempted and may have ultimately worsened the outcome for these cases.

Steroids are used frequently as the mainstay for induction of remission in moderate to severe active IBD in people. Currently it is not known exactly what effect steroids have on the pancreas as controversy surrounds the diagnosis of steroid-induced pancreatitis. In our study population, we did not find any significant difference in the frequency of steroid treatment between the two groups (*P*=0.13), implicating that steroid treatment had no effect on the pancreas in these dogs. However, a prospective study would be needed to investigate if steroid treatment in IBD patients is a risk factor for the development of pancreatitis.

In conclusion, this study suggests that inflammatory bowel disease-associated pancreatic inflammation does exist in dogs. Canine IBD-CP is most commonly subclinical and is easily missed by routine diagnostic tests used in dogs suspected of IBD. It is important to diagnose concurrent pancreatitis in dogs with IBD as concurrent pancreatitis is associated with a worse outcome. The etiology of canine IBD-CP is unknown and further studies are needed to establish the cause and appropriate treatment.

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CANINE IBD: NEW OPTIONS FOR DIAGNOSIS, PROGNOSIS, & THERAPY

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Among the causes for chronic enteropathies in dogs, adverse reactions to food, idiopathic inflammatory bowel diseases (IBD), and antibiotic-responsive diarrhea (ARD) are common. These disorders are retrospectively diagnosed by their response to treatment.

The clinician faced with a referral case usually performs an extensive workup to exclude extra-gastrointestinal causes as well as easily treatable disorders such as pancreatic diseases, chronic parasitic or bacterial infections, and tumors. After taking intestinal biopsies and reaching a diagnosis, the usual approach to treatment is a trial therapy with elimination diet, antibiotic treatment for several weeks, and, finally, immunosuppressive treatment with corticosteroids. Some recent large prospective studies have shed some light on the usefulness of tests that are routinely performed during the workup of cases with chronic diarrhea, and several tests have been found to be useful for prognosis.

DIAGNOSTIC TOOLS: CLINICAL ACTIVITY INDICES FOR CANINE IBD

In human medicine, indices for clinical activity of disease are calculated for patients before, during, and after therapy, therefore enabling the comparison of clinical severity over time and between different patients. These indices are calculated based on clinical symptoms (frequency of diarrhea, blood in the feces, abdominal cramping, systemic symptoms associated with IBD) and serum markers such as C-reactive protein (CRP) and albumin measurement. A recent study describes the applicability of a clinical index of disease for canine cases (Canine IBD Activity of Disease Index, or CIBDAI). Six gastrointestinal parameters (attitude/activity, appetite, vomiting, stool consistency, stool frequency, and weight loss) are evaluated and scored from 1 to 3 and added up to a composite score of 0 to 3 for insignificant disease, 4 to 5 for mild IBD, 6 to 8 for moderate IBD, and 9 or greater for severe clinical IBD. In the study of Jergens et al, 58 dogs with a median CIBDAI of 5.5 were re-evaluated after 2 to 3 weeks of treatment, and were found to have a significantly decreased CIBDAI to a median of 1.6.

These findings were reproducible in a study performed by the author in Bern, Switzerland. In 42 dogs with diet-responsive disease, median CIBDAI decreased significantly from 6.3 before to a median of 1.2 after treatment. In the 23 dogs with steroid-responsive disease, median CIBDAI was higher before starting treatment (CIBDAI 9.2) and decreased only into the range of moderate disease activity after treatment (CIBDAI 5.5).

We also evaluated the CIBDAI and additional parameters such as albumin measurements, assessment of the degree of peripheral edema and ascites, as well as severity of pruritus for their prognostic value regarding outcome. Thirteen of 70 (18%) dogs were euthanized due to intractable disease. Univariate analysis identified a high clinical activity index, high endoscopic score in the duodenum, hypocobalaminemia (<200 ng/L) and hypoalbuminemia (<20 g/L) as risk factors for negative outcome. Based on these factors, a new clinical scoring index (Canine Chronic Enteropathy Activity Index, or CCECAI) was defined which predicts negative outcome in dogs suffering from chronic enteropathies with very good sensitivity and specificity (0.95%). Four categories of severity were defined for the CCECAI: insignificant disease: 0–3, mild disease: 4–5, moderate disease: 6–8, severe disease: 9–11, very severe disease: ≥12. If a dog scores over 12 with this clinical activity index, its risk for being euthanized due to refractory disease is increased 64-fold.

The CIBDAI and CCECAI are compared in Table 1.

Histology and T-Cell Staining

Sampling of intestinal biopsies is considered to be an essential step to exclude neoplastic causes and confirm the presence of intestinal inflammation. However, the interpretation of intestinal biopsies is difficult and subject to controversy. No clearly defined criteria exist to date on which the pathologist can reliably base his decision. The grading scheme proposed by Jergens et al subjectively describes mild lesions as those with no mucosal disruption and only mild infiltration with inflammatory cells, severe lesions as those with architectural distortion of the mucosa, and severe infiltration with inflammatory cells, and moderate histologic severity as those lesions showing intermediate changes between mild and severe. Immunohistochemically, increased lamina propria CD_3 cells, especially of the α/ß-subtype, and increased CD_4 T cells, are found in canine IBD, suggesting that T cells may be crucial in the pathogenesis of the disease.

In our studies, we found no correlation of CIBDAI with histologic grading before or after therapy for IBD. In addition, total lymphocyte counts as well as the number of infiltrating CD_3 cells in the lamina propria were not different before and after treatment. This is a new and unexpected finding which suggests that the type and degree of histological infiltrates in canine IBD may not be as helpful as in human medicine, where the clinical scores correlate very well with the histological grading. Clearly, new and more defined criteria for histological assessment of intestinal biopsies from dogs with IBD are needed.

Measurements of Cytokines

Based on histologic and immunohistochemical studies of IBD in dogs, the production of pro-inflammatory (Th_1)-cytokines was for a long time regarded as the main pathogenetic mechanism of disease, comparable to the situation in human Crohn's disease. Several recent studies investigated the cytokine mRNA pattern in intestinal biopsies in dogs with chronic enteropathies. Earlier studies measuring cytokine expression semi-quantitatively found increased levels of interferon gamma

Table 1. Comparison of Clinical Activity Indices for Canine IBD

Canine IDB Activity Index (CIBDAI)	Canine Chronic Enteropathy Activity Index (CCECAI)
Attitude/Activity	**Attitude/Activity**
0 Normal	0 Normal
1 Slightly decreased	1 Slightly decreased
2 Moderately decreased	2 Moderately decreased
3 Severely decreased	3 Severely decreased
Appetite	**Appetite**
0 Normal	0 Normal
1 Slightly decreased	1 Slightly decreased
2 Moderately decreased	2 Moderately decreased
3 Severely decreased	3 Severely decreased
Vomiting	**Vomiting**
0 Normal	0 Normal
1 Mild (1x per week)	1 Mild (1x per week)
2 Moderate (2-3x per week)	2 Moderate (2-3x per week)
3 Severe (>3x per week)	3 Severe (>3x per week)
Stool Consistency	**Stool Consistency**
0 Normal	0 Normal
1 Slightly soft feces	1 Slightly soft feces
2 Very soft feces	2 Very soft feces
3 Watery diarrhea	3 Watery diarrhea
Stool Frequency	**Stool Frequency**
0 Normal	0 Normal
1 Slightly increased (2-3 x per day) or fecal blood, mucus or both	1 Slightly increased (2-3 x per day) or fecal blood, mucus or both
2 Moderately increased (4-5 x per day)	2 Moderately increased (4-5 x per day)
3 Severely increased (>5x per day)	3 Severely increased (>5x per day)
Weight Loss	**Weight Loss**
0 None	0 None
1 Mild (<5%)	1 Mild (<5%)
2 Moderate (5-10%)	2 Moderate (5-10%)
3 Severe (>10%)	3 Severe (>10%)
	Albumin Levels
	0 Albumin >20 g/L
	1 Albumin 15-19.9 g/L
	2 Albumin 12-14.9 g/L
	3 Albumin < 12 g/L
	Ascites and Peripheral Edema
	0 None
	1 Mild ascites or peripheral edema
	2 Moderate amount of ascites/ peripheral edema
	3 Severe ascites/pleural effusion and peripheral edema
	Pruritus
	0 No pruritus
	1 Occasional episodes of itching
	2 Regular episodes of itching, but stops when dog is asleep
	3 Dog regularly wakes up because of itching

(IFN-γ), tumor necrosis factor (TNF), interleukin-2 (IL-2), IL-5, IL-12, and transforming growth factor–beta (TGF-β) suggesting a similar Th_1-biased cytokine profile in dogs with IBD. However, newer studies in which real-time reverse transcriptase polymerase chain reaction (RT-PCR) was used to measure cytokine expression profiles in biopsies found no distinct cytokine profile towards either a Th_1 or Th_2 pattern. Furthermore, when cytokine mRNA levels were compared with total number of infiltrating cells and CD_3 cells as well as CIBDAI, no significant correlations of cytokines levels with any of these parameters were detected.

With current methodologies, it seems unlikely that cytokine measurements may help to differentiate between food-responsive and steroid-responsive enteropathies or as prognostic markers during the progression of disease. In the future, investigation of the cytokine profile on a single cell level by measuring intracellular cytokine levels using flow cytometry may prove to be more useful than investigating whole biopsy expression profiles.

Albumin

Decreased albumin levels have been described as a negative prognostic indicator in a recent retrospective study of canine IBD. Protein-losing enteropathy accounts for the loss of albumin through the gut mucosa in severely affected dogs with IBD. One study described 12/80 (16%) dogs with hypoalbuminemia and 4/80 (5%) dogs with panhypoprotenemia. Seven of these 12 dogs subsequently had to be euthanized for intractable IBD.

In the dogs of our study, 12/58 (21%) cases initially presented with hypoalbuminemia. Of these 12 dogs, 7 were panhypoproteinemic with severe hypoalbuminemia (mean albumin level 11g/L) and 3 of those eventually had to be euthanized. This reiterates the importance of measuring albumin in cases with IBD, as it is also a prognostic indicator, especially when it drops to lower than 15 g/L. However, 8 of 12 dogs from our study were successfully treated with cyclosporine after failing to respond to steroid treatment. This suggests that early aggressive treatment in hypoalbuminemic dogs may potentially decrease mortality rates in severely ill animals.

C-Reactive Protein (CRP)

CRP is a serum acute phase protein which is elevated in numerous different diseases. In people with IBD, several indices of clinical activity of disease incorporate measurements of CRP in their calculation. The human Crohn's disease activity index includes assessment of clinical parameters as well as albumin and CRP measurements, and this index correlates well with histologic severity of disease. In dogs, a similar correlation between CIBDAI and CRP measurements has been found in one large study incorporating 58 dogs. CRP was elevated in the 28 dogs with CIBDAI scores above 5 (at least mild disease activity) compared with normal dogs and decreased significantly after treatment.

In our experience, CRP does not seem to be very helpful when assessing dogs with chronic enteropathies. CRP was measured in 21 dogs with IBD before treatment and in 18 dogs after treatment. Based on established reference ranges, CRP was only elevated in 6/21 dogs before treatment and did not correlate with CIBDAI or histologic scoring.

Based on available published data, it is possible that CRP is useful as an additional assessment tool in severely ill patients, even though a large percentage of dogs with IBD do not show any elevations in CRP. Interpretation of elevated levels may also be hampered by increases of CRP related to other diseases than IBD.

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TREATMENT OF CANINE IBD WITH CYCLOSPORINE

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THERAPY OF CANINE IBD

The traditional approach to the treatment of canine inflammatory bowel disease (IBD) relies on three components that can be used individually or most often combined: dietary modifications, antibiotic treatment, and specific anti-inflammatory and immunosuppressive drugs. Although most specialists agree that dietary therapy is a central component, the routine use of antibiotics in the treatment of dogs tentatively diagnosed with IBD is subject to controversy. In many instances, immunosuppressive doses of corticosteroids are administered for various lengths of time.

In a prospective study of 57 dogs with chronic intestinal disease of more than 3 weeks' duration, 36 dogs responded totally or significantly to one week of a food trial with a salmon- and rice-based commercial elimination diet alone (dry formulation). The high proportion of food responsive disease (63%) was surprising considering that many of these dogs had been referred by veterinarians who had previously attempted dietary and medical treatment without satisfactory outcome. This observation has also been made by gastroenterologists working in other referral centers. Upon presentation, our food responders were significantly younger than the dogs that did not respond to dietary therapy and required medical therapy (median age 2 years vs. 6 years). There is currently a wide variety of commercially available diets to recommend for elimination trials: hydrolyzed diets are a recent alternative to classical diets offering a novel protein source

Infections with enteropathogenic bacteria such as *Campylobacter* sp. are unlikely to be misdiagnosed as IBD if a systematic diagnostic approach is applied. However, it remains unclear in many instances whether the bacteria are the cause of the disease or merely grow opportunistically in dogs with underlying enteropathies.

The existence of primary idiopathic small intestinal bacterial overgrowth (SIBO) is subject to controversy. The more generic denomination *idiopathic antibiotic-responsive diarrhea* (ARD) is currently preferred. ARD is most commonly recognized in young German shepherds with chronic intermittent diarrhea. It is diagnosed based on signalment, history, and clinical signs, as well as on response to an empiric course of oral antibiotics (eg, oxytetracycline 10—20 mg/kg TID, or metronidazole 10–20 mg BID, or tylosin 20 mg/kg BID to TID).

ANTI-INFLAMMATORY AND IMMUNOSUPPRESSIVE TREATMENT

Current treatment protocols for canine IBD most often involve the use of immunosuppressive doses of corticosteroids for several weeks followed by slow tapering to reduce the intestinal mucosal inflammation and achieve clinical remission. The usual protocols for prednisolone recommend dosages of 1–2 mg/kg BID for approximately 2 to 4 weeks, followed by a slow tapering period over weeks to months. However, a number of dogs treated with immunosuppressive doses of corticosteroids will show either no response at all to the drug or will relapse after weeks to months of treatment. A recent retrospective study including 80 dogs with IBD revealed 13/80 or 16% of cases with intractable disease. In people, failure to respond to medical treatment with steroids can be observed in 20% to 30% of patients with IBD.

At high dosages, corticosteroids have numerous side effects such as polyuria/polydipsia (PU/PD), which may become unbearable for the owners, especially in large breed dogs. In difficult cases that require prolonged corticosteroid therapy but are sensitive to its side effects, the more expensive drug budesonide has been used with some anecdotal success (3.0 mg/m, resp. 0.5–3.0 mg per dog, depending on body weight, once daily or every other day). In humans, budesonide undergoes a first-pass hepatic extraction of approximately 80% to 90%. Therefore, only a fraction of the absorbed compound reaches the systemic circulation, theoretically decreasing side effects. It has been documented that budesonide suppresses the hypothalamic-pituitary-adrenal axis in dogs with IBD. A well-designed prospective study comparing prednisone and budesonide in the treatment of canine IBD is needed.

Other immunosuppressive agents such as azathioprine, chlorambucil, and cyclophosphamide at the usual dosages are used alone or in combination with corticosteroids. When used in combination, they may (a) decrease the required dosage of corticosteroids and the associated side effects, or (b) allow the dogs to be weaned off corticosteroids as soon as possible. Moreover, these drugs are also used cases of steroid-refractory canine IBD. They may have a delayed onset of action (weeks to months until maximal effect). To date, there are no publications objectively comparing the efficacy of these different drugs.

If the disease is limited to the large bowel, compound molecules containing meselamine (5-ASA) such as sulfasalazine (initially 10–25 mg/kg PO TID for 6 weeks, then taper down) or olsalazine (initially 5–10 mg/kg PO TID, then reduce gradually) have proven beneficial effects on the colonic mucosa. Keratoconjunctivitis sicca is a well known complication in dogs treated with either of these two drugs.

CYCLOSPORINE IN IBD: EXPERIENCE WITH HUMAN AND CANINE PATIENTS

Cyclosporine A (CyA) has been shown to be effective in steroid-refractory attacks of human IBD and may also be a valid alternative for canine IBD.

The cellular infiltrate in canine chronic idiopathic enteropathies mainly consists of lymphocytes and plasma cells in the lamina propria. The anti-inflammatory effect of CyA in IBD is thought to be due to its action on T cells that infiltrate the mucosa. CyA binds intracellularly to calmodulin, which reduces the release of calcium from the endoplasmic reticulum, thereby inhibiting further downstream signaling and, finally, inhibiting the expression of interleukin-2 (IL-2). Since IL-2 is necessary for the survival of T cells for longer than 24 to 48 hours, it is hypothesized that CyA decreases the number of infiltrating T cells in the mucosa of the dogs, thereby reducing the amount of pro-inflammatory cytokines and, finally, the clinical signs of the disease. For dogs, cyA is currently only approved as an oral formulation. This raises the concern that severely ill dogs with inflammatory duodenal infiltrates will not absorb enough drug to produce a clinical effect.

We performed a pilot study to evaluate the pharmacokinetics and clinical efficacy of CyA in dogs with severe steroid-refractory clinical IBD. A total of 14 dogs were included into the clinical efficacy study. All of these dogs had been treated with 2 mg/kg per day of prednisolone PO for a period ranging from a minimum of 6 weeks with only minimal clinical effect before being tapered off. The severity of disease was assessed using the canine IBD activity index (CIBDAI) described by Jergens et al, with a score of 0–3 indicating clinically insignificant disease, a score of 4–5 indicating mild IBD, a score of 6–8 indicating moderate IBD and a score of >9 indicating severe clinical IBD. After the first endoscopic examination, all dogs received treatment with CyA 5 mg/kg PO once daily for a total of 10 weeks and CIBDAI scores were assessed every second week after starting treatment during the entire study period. A recheck endoscopic examination was performed in 9 dogs after 10 weeks of treatment. In addition, serum concentration of CyA was measured in 8 dogs by FPLI during the 24 hours after giving the first dose of CyA to assess the drug pharmacokinetics.

Clinical severity as scored by CIBDAI was very high (over 9) in the majority of cases at the beginning of treatment with CyA, indicating severe clinical disease. After 10 weeks of treatment with CyA, the median CIBDAI was significantly reduced. Eight dogs showed a complete response within 4 weeks of treatment (reduction in CIBDAI to a score of 0–2). Two dogs did not respond to treatment with CyA during the first 10 weeks of the study and were euthanized 6 and 10 weeks, respectively, after starting treatment with CyA. One dog responded well to CyA for 14 weeks but then experienced a relapse with clinical signs of intractable vomiting and was euthanized at that time. Side effects attributed to CyA during the study transiently occurred over the first two weeks of treatment. Reported side effects were vomiting and partial anorexia in 4 of 14 dogs, gingival ulceration in one dog, and alopecia followed by hypertrichosis in one dog.

Pharmacokinetics of CyA in severe canine IBD were comparable to values in normal dogs and atopic dogs, indicating that CyA can be expected to be effective in severely ill IBD cases from the first day of treatment.

CyA was effective in reducing clinical signs of severe IBD in a majority of dogs in this pilot study and may therefore be a valid option for steroid-resistant dogs with IBD.

CONCLUSION

Our understanding of canine IBD has considerably improved in the last decade; however, numerous questions still need to be answered. Many options for treating the disease are available. Based on the variety of cases seen by a particular veterinarian, different routine treatment protocols are recommendable. Our original study describing the use of cyclosporine in dogs with IBD clearly documents the efficacy of this substance. Many additional "new" drugs can be found on the market. However, objective and scientifically sound investigations are still lacking to support their use in clinical situations. Therefore, veterinarians often have to rely solely on anecdotal evidence from colleagues and accrued personal experience to guide them while they elaborate a treatment plan.

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FELINE MEGACOLON

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Constipation in cats is a difficult problem that can become permanent and debilitating in the form of megacolon. This discussion focuses on the diagnosis and stepwise treatment of megacolon in cats.

DIAGNOSING MEGACOLON

The predominant clinical sign exhibited by cats developing megacolon is chronic constipation. Owners see cats spending inordinate amounts of time in the litterbox, often with straining and vocalization. Stools passed are often hard and small.

On physical examination, cats may be depressed, and may be dehydrated. The colon is full of hard, impacted fecal material. Laboratory work, if performed, may reflect dehydration.

Radiographs help make the differentiation between simple constipation and megacolon. Fecal material within the colon acts as a radiographic contrast material, outlining the extent of colonic dilation. If the colon is abnormally dilated, then the diagnosis is megacolon.

TREATMENT OF ACUTE OBSTIPATION

Treatment of megacolon involves two phases: relief of the acute colonic impaction (known as obstipation), and long-term treatment of the megacolon. Relief of obstipation is essential.

Fluid therapy is important, since many obstipated cats are dehydrated. With dehydration, fluid is shifted from the colon to the interstitium, further worsening the impaction.

Enemas are required to soften and help with passage of the fecal mass. Enema solutions with dioctyl sodium succinate or lactulose may be helpful.

Occasionally, the cat must be anesthetized, and the fecal mass gently broken up to allow for passage. This manual disimpaction procedure can be difficult and time-consuming, as well as unpleasant. Cats are at risk of developing sepsis, and often require hospitalization.

Once the obstipation is relieved, long-term treatment is required. Because of the effects and costs of relief of acute obstipation, great effort should be made towards successful long-term treatment.

LONG-TERM TREATMENT

Follow-up treatment of cats with megacolon is essential in order to prevent further bouts of obstipation. Treatment starts with dietary manipulations only and then progresses as the cat's condition warrants.

Dietary Fiber

Adding fiber to the diet provides bulk to the stool, traps water, and provides substrate for bacterial fermentation. The cat can be switched to a high-fiber diet, or a fiber source can be added to the diet. Examples of fiber sources include canned pumpkin, wheat bran, or commercially available psyllium preparations marketed for constipation in people.

Osmotic Laxatives

If fiber alone is insufficient to control constipation associated with megacolon, then the next step is to add an osmotic laxative such as lactulose. Lactulose is a disaccharide that is not digested by mammals. It is broken down by colonic bacteria, creating an osmotic pull for water into the feces. Particularly if fiber is present in the feces, this osmotic pull of water into the feces allows for improved fecal quality.

Motility Modifiers

Cisapride, a benzamide serotonin 5 HT-4 agonist, stimulates smooth muscle contractions in the colon. It no longer is marketed in the US, but can be obtained through compounding pharmacies. It is particularly helpful in cats with megacolon that no longer respond to dietary therapy alone. Newer drugs are also being released and tested, such as tegaserod (which has been shown to normalize intestinal transit in dogs with opioid-induced bowel dysfunction when dosed at 3–6 mg/kg) and prualopride. Unfortunately, cats with megacolon often become refractory to the effects of drugs such as cisapride.

Surgery

Despite the best in medical therapy, some patients (particularly cats with longstanding megacolon) require surgery. Subtotal colectomy is the procedure of choice, and, if possible, the ileocecal valve is left in place. Most cats will initially have some diarrhea following the procedure, and will later have frequent, somewhat loose stools. Owner satisfaction following the procedure seems to be quite high.

If anything, this surgery is underutilized for cats with megacolon since the veterinary community adopted the routine use of cisapride. Owners spend large amounts of money treating cats for repeated bouts of obstipation despite appropriate long-term medical intervention.

In summary, megacolon is a frustrating disease for cats, owners, and veterinarians alike. Treatment is aimed at progressively altering stool consistency, followed by intestinal motility. When those manipulations fail, subtotal colectomy is a viable option for treatment, often leaving cats with several slightly loose stools per day.

CONSTIPATION — WHEN THE MOVEMENT NEEDS IMPROVEMENT

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The sins of the colon are its diseases. But I sometimes wonder whether it is not more sinned against than sinning, for what with attacks from above with purges, attacks from below with douches, and frontal attacks by the surgeons, its sorrows are numerous and real.
—A.F. Hurst, 1922

DEFINING CONSTIPATION

Constipation is a gastrointestinal disease of great impact in both humans and companion animals in developed countries today. Millions of dollars are spent annually on over-the-counter laxative products for humans, and many owners are acutely aware of any abnormal bowel habits which may occur in their pets.

Constipation is difficult to define. In humans, it is a symptom characterized by the infrequent passage of small, hard stools with increased straining and pain. In small animals, it is defined as the infrequent passage of stools with increased straining, although some animals do not exhibit obvious signs. Obstipation is severe constipation requiring interventional therapy (such as enemas) for relief. Megacolon is irreversible dilation of the colon. While almost all animals with megacolon are constipated, few constipated animals have megacolon.

NORMAL COLONIC ANATOMY AND PHYSIOLOGY

The large intestine of dogs and cats consists of the cecum, colon, rectum, and anal canal. Each segment consists of four layers: mucosa, submucosa, muscular layer, and serosa. The muscular layer is further subdivided into inner circular and outer longitudinal layers. In contrast to other species, the colon of dogs and cats is relatively short.

The anal canal is surrounded by the internal anal sphincter (a thickened area of smooth muscle within the circular muscle layer) and the external anal sphincter (which is composed of skeletal muscle). The rectococcygeal, levator ani and coccygeus muscles promote fecal propulsion via movement of the tail and perineum.

The large intestine is primarily innervated by the parasympathetic nervous system, and the destruction of pelvic nerve parasympathetic flow decreases rectal sensation, resulting in constipation. The large intestine also contains an intrinsic nervous system that affects colonic motility via the myenteric and submucosal plexuses. Disorganization or damage of the myenteric plexus is also associated with constipation.

Colonic motility is integral to the proper functioning of the large intestine. Two patterns of motility are observed: propulsive and nonpropulsive. Propulsive contractions are primarily mass movements, which are strong contractions stimulated by food and somatic activity. Nonpropulsive contractions are primarily segmental contractions of the circular smooth muscle layer, which mixes colonic contents and ensures adequate mucosal contact of the colonic contents.

The integration of colonic motility is a function of the intrinsic myoelectric activity of the colon. As with other areas of the gastrointestinal tract, the colon exhibits a basal electrical rhythm (BER) of electrical potential change in smooth muscle cell membranes. The BER arises from pacemakers in the circular muscle layer of the colon and propagates the electrical potential for variable distances along the colon. Multiple pacemakers with different BER frequencies direct myoelectric activity into forming either a segmental or propulsive contraction. For example, a dominant pacemaker in the ileocecal area of cats has been shown to propagate a contraction that forces ileal effluent into the cecum, whereas when a cecal pacemaker becomes dominant, contents are forced distally into the colon.

The colon functions in fecal processing and elimination. A major role is the absorption of water and electrolytes from the relatively liquid ileal contents. The colonic mucosa actively transports sodium and chloride from the lumen into the interstitial spaces and water is passively reabsorbed in response. In addition, the colonic mucosa secretes mucus for lubrication and easier fecal passage.

The colon is the only site in dogs and cats where bacterial fermentation of ingesta normally occurs. Although the large intestinal tracts of dogs and cats are relatively short, large numbers of anaerobic bacteria inhabit the colon. Dietary fiber is the primary substrate for fermentation in the colon of small animals. Although little nutritional benefit is derived from this fermentation, it promotes fecal bulk by increasing colonic bacterial numbers and retaining fecal water.

Fecal storage is another important colonic function. Defecation is a reflex action in response to rectal luminal distention. The urge to defecate is triggered by increased tension in the rectal wall; the receptors are extrarectal and transmission of this sensation is carried along parasympathetic pathways. The defecation reflex can be inhibited or delayed by overriding cerebral input, thus allowing feces to be retained for long periods if the dog or cat perceives that the environment is not appropriate for defecation.

Passage of a stool through the anal canal requires relaxation of both the internal and external anal sphincters. The internal anal sphincter relaxes by a myenteric reflex when the rectum is distended (the recto-anal distension reflex). The external anal sphincter contracts when the rectum is distended (the recto-anal contractile reflex), but relaxation of the external sphincter can occur voluntarily, coinciding with intra-abdominal pressure, or when the rectum is massively distended.

PATHOPHYSIOLOGY OF CONSTIPATION

Any event that slows colonic motility or blocks colonic outflow may result in constipation. Several categories of disease that can cause constipation are listed below.

Environmental Factors

Many animals will ignore the urge to defecate if they are uncomfortable with their surroundings. This frequently occurs if the animal is in a different habitat, such as a veterinary hospital. Some cats will refuse to defecate in a soiled litter box.

Pain-Induced Causes

Dogs or cats that suffer pain when attempting to defecate may suppress this urge, resulting in increased colonic fecal retention time. This allows greater resorption of water through the colonic mucosa, eventually causing constipation. Thus, any anorectal disease associated with pain (such as perianal fistulas, anal sacculitis, or pelvic fractures) can cause constipation.

Intraluminal Colonic Obstruction

Ingested material, such as bones, hair, or plant material, may mix with feces and cause colonic impaction. Intraluminal colonic tumors, polyps, or granulomas may obstruct fecal outflow. Rectal diverticuli and perineal hernias may also impair fecal passage.

Extraluminal Colonic Obstruction

Causes of extraluminal colonic obstruction include prostatomegaly, malunion of pelvic fractures, and extraluminal neoplastic masses. Occasionally, matting of perineal hair will obstruct defecation and produce constipation (pseudocoprostasis).

Metabolic Disease

Dehydration may induce constipation by promoting excess fluid shifts from the feces to the colonic interstitium. Electrolyte disturbances, particularly hypokalemia and hypercalcemia, may also alter colonic motility.

Neurologic Disease

Damage to the sacral spinal cord, cauda equine region, or pelvic nerves can cause decreased rectal sensation and constipation. Chagas' disease, an uncommon trypanosomal disease of dogs transmitted by Reduviidae beetles, may destroy the myenteric plexuses and cause constipation and megacolon.

Muscular Disease

Cats with idiopathic megacolon have been shown to have abnormal colonic muscle function in isometric stress tests when compared to colonic muscle from normal cats. In addition, their colonic muscle did not respond normally to several neurotransmitters.

Iatrogenic Causes

Several medications used in small animal medicine can cause constipation. These include some types of opioids, antacids, anticholinergics, anticonvulsants, bismuth preparations, diuretics, iron preparations, and sucralfate.

DIAGNOSTIC APPROACH TO CONSTIPATION

The first step in evaluating the constipated animal is a review of the signalment and history. Constipation is often a condition in older pets with limited activity. Some diseases associated with constipation may occur in a particular breed or sex (eg, perianal fistulas in German shepherd dogs, or perineal hernias in older male dogs). The dietary history, including any ingestion of foreign material, is needed. History of weight loss or systemic illness may also help identify metabolic or neoplastic causes of constipation. Frequency and consistency of bowel movements should be recorded, including the presence of fecal blood, which may increase the suspicion of intraluminal trauma or mass lesions. Finally, prescribed and over-the-counter drugs administered to the pet should be considered.

A physical examination is needed, during which careful attention should be given to the perineal area in order to rule out perineal hernia, anal sacculitis or abscess, anal strictures, perianal fistulas, or other diseases obstructing defecation or causing pain. A neurologic examination is important to eliminate a possible underlying neurologic disease. A digital rectal examination (in dogs) should attempt to identify anal strictures, perineal hernias, intraluminal masses, foreign bodies, prostatomegaly, malunion of pelvic fractures, extraluminal rectal impingement by intrapelvic masses or iliac lymphadenopathy. The character of the stool should be recorded and any bones, mats of hair, or other abnormalities noted.

Hematologic and serum biochemical evaluation may be helpful. Evidence of inflammation may help identify anal sac abscessation, inflammation associated with neoplasia, or other diseases associated with pain or colonic obstruction. Metabolic causes for constipation, such as dehydration, hypokalemia, and hypercalcemia may be detected.

Abdominal radiographs may identify megacolon, malunion of pelvic fractures, prostatomegaly, and abdominal masses. Occasionally, evacuation of the colon and contrast radiography (barium enema), while the animal is under general anesthesia are required to identify intraluminal colonic masses, but this technique has largely been replaced by colonoscopy.

Colonoscopy can be used to identify intraluminal foreign bodies, mess lesions, and strictures. Colonoscopic biopsies of masses can also provide a histopathologic diagnosis, which is helpful for planning surgery. Colonoscopy requires evacuation of the colon of feces by using enemas and/or oral cathartic solutions.

TREATMENT OF CONSTIPATION

If possible, treatment is aimed at correcting the underlying cause for the constipation. Unfortunately, no specific treatment is available in many cases. When this occurs, symptomatic care is warranted. Initially, the goal is the removal of feces from the colon, followed by steps to prevent recurrence of constipation.

Fluid Therapy

Fluids often help soften the stool in dehydrated patients, and evacuation of the colon is facilitated if the patient is adequately hydrated. Intravenous or subcutaneous fluids are preferred over oral rehydration in these patients.

Enemas

Enemas are needed in severely constipated animals to evacuate the colon. Several types of enema solutions can be used. Warm water is often sufficient. Dioctyl sodium sulfosuccinate (DSS) is an emollient that may be added in small amounts (5–10 mL/L) to the enema solution in order to facilitate softening of the stool. Although mild soap solutions have been routinely used for enemas in small animals with few reported untoward effects, in humans they may cause colitis, and even death has been reported. Commercially available enemas containing phosphate salts may induce potentially fatal electrolyte disturbances in cats and small dogs and should be avoided.

Suppositories

Glycerine, bisacodyl, and DSS preparations are available as rectally administered suppositories for treatment of constipation. These are helpful only in mild cases of constipation, but not in obstipation.

Laxatives

There are many types of laxatives available over-the-counter that pet owners may use on their dog or cat, and some laxatives made specifically for pets. Most laxatives can be classified based on their mode of action.

- **Bulk-forming laxatives.** These use dietary fiber to treat and prevent constipation. Insoluble fiber absorbs large quantities of water, provides substrate for colonic bacteria to multiply, and adds to fecal bulk. This creates a bulkier, softer stool that is easier to pass. Examples include many high fiber pet foods, canned pumpkin, bran, and commercial psyllium products.
- **Emollient laxatives.** These are surfactants that facilitate the mixing of aqueous and fatty substances in the stool, resulting in a softer stool. As previously mentioned, DSS is an emollient that can be added to an enema or can be given orally. Emollients are useful in the short-term management of constipation, but less helpful with long-term constipation.
- **Lubricant laxatives.** Lubricant laxatives coat the fecal mass and reduce resorption of water. Although mineral oil is commonly used in humans for this purpose, its use should be avoided (if given as a bolus) because of the risk of aspiration. Flavored petroleum jelly products are marketed for pets as lubricant laxatives.
- **Oral saline laxatives.** Magnesium hydroxide and magnesium sulfate preparations are severe cathartics, reserved for suspected poisonings. They should not be used chronically in animals.
- **Stimulant laxatives.** Some types of stimulant laxatives available for humans, the anthroquinones, cause damage to the myenteric plexus and cause an increasingly unresponsive dependence on the laxative. In general, stimulant laxatives should be avoided in small animals, although bisacodyl, a drug which stimulates colonic smooth muscle contractility, can be used safely on an occasional basis.
- **Hyperosmotic laxatives.** These laxatives increase intraluminal pressure by their osmotic properties, thus stimulating peristalsis. Lactulose, for example, is a disaccharide catabolized by colonic bacteria to short-chain carboxylic acids which exert an osmotic effect to induce laxation.

Motility Modifiers

Cisapride, a benzamide serotonin 5 HT-4 agonist, stimulates smooth muscle contractions in the colon. It no longer is marketed in the US, but can be obtained through compounding pharmacies. It is particularly helpful in cats with recurrent constipation that no longer respond to dietary therapy alone. Newer drugs are also being released and tested, such as tegaserod (which has been shown to normalize intestinal transit in dogs with opioid-induced bowel dysfunction when dosed at 3–6 mg/kg) and prualopride.

Surgery

Despite the best in medical therapy, some patients (particularly cats with longstanding megacolon) require surgery. Subtotal colectomy is the procedure of choice, and, if possible, the ileocecal valve is left in place. Most cats will initially have some diarrhea following the procedure, and will later have frequent, somewhat loose stools. Owner satisfaction following the procedure seems to be quite high.

UPDATE ON FELINE INFLAMMATORY BOWEL DISEASES

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Feline inflammatory bowel diseases (IBD) are an idiopathic condition characterized by infiltration of the gastrointestinal mucosa with various inflammatory cells, mostly lymphocytes and plasma cells, but occasionally eosinophils or other leukocytes. The associated clinical signs are usually compatible with a variety of diseases of the gastrointestinal tract and other organ systems. Therefore, these conditions must be ruled out prior to contemplating the diagnosis of IBD.

It is surprising to see how few contributions have been made to the literature on this important topic. Several case series were published over the last 15 years, and preliminary work investigating pathogenesis was also performed. Fortunately, additional studies are currently underway or in the publication review process. It is hoped that they will contribute to further our understanding of feline IBD, and identify clinically useful tools to facilitate our diagnostic and therapeutic approach of affected cats.

ETIOLOGY

The etiology of feline IBD remains largely unknown. Based on studies performed on various rodent animal models of human IBD, several factors seem to be implicated in the pathogenesis of intestinal inflammation. In the last decade, much research has focused on abnormal interactions between intestinal microbial flora and the cells of innate and acquired immune system in the gastrointestinal mucosa. A possible key to the enigma, genetic mutations affecting important pathways for the recognition of bacteria by the innate immune system have been shown to predispose people to Crohn's disease, one of the two forms of human IBD.

Classically, Crohn's disease is associated with a Th1 immune response while inflammation in ulcerative colitis, the other form of human IBD, is driven by a Th2 response. Two independent groups have attempted to identify the preponderant cytokines in the intestinal mucosa of cats. There was concurrent activation of both pro-inflammatory and immunomodulatory cytokines, and the immune reactions associated with feline IBD could not be classified as Th1 or Th2. It was hypothesized by one researcher that the pattern may reflect activation of epithelial cells by gram-negative bacteria. In addition, an increase in class II MHC expression was documented the mucosa in cats with IBD, suggesting intense antigen processing and presentation by macrophages and intestinal epithelial cells. It is probable that feline IBD represents a group of diseases of different etiology resulting in intestinal mucosal inflammation.

CLINICAL PRESENTATION

Cats affected with IBD are usually middle-aged to older animals, but the age range is wide and includes very young animals. There is no documented breed predilection, although purebred cats such as Siamese, Persians, and Himalayans may be at increased risk, and no sex predilection. Clinical signs reported in several published clinical studies are summarized in Table 1. It is noteworthy that diarrhea, a typical sign of intestinal disease in dogs, is present in less than one half of cats with IBD (37% to 50%). The most commonly observed signs are vomiting, weight loss, and anorexia. In one study, cats that had lost weight over long periods of time had more severe inflammatory lesions in their intestinal mucosa. This is of interest because many cats show waxing and waning signs, and their owners seek veterinary attention only late in the course of disease. In another study, type and frequency of clinical signs did not allow distinguishing cats with IBD from those with gastrointestinal lymphoma.

DIAGNOSTIC APPROACH

The diagnosis of feline IBD is reached by exclusion. Especially in older cats, all diseases that may cause a similar clinical picture must be systematically ruled out. They include (but are not restricted to) endocrine diseases such as hyperthyroidism and diabetes mellitus, chronic kidney disease, liver diseases, exocrine pancreatitis, and heartworm infestation. In addition, other gastrointestinal diseases such as adverse reaction to food (including food intolerance and food allergy), parasite infestation (worms and protozoa such as *Giardia* and *Tritrichomonas* that are usually more prevalent in cattery situations), fungal infections (eg, histoplasmosis), and gastrointestinal lymphoma may also present with the same clinical signs.

Twenty seven (49%) of 55 cats presented in New Zealand with chronic gastrointestinal signs similar to those described in Table 1 were diagnosed as "food responsive" based on improvement or resolution of signs after being fed a novel protein diet. Sixteen of 29 (55%) were classified as food sensitive due to recurrence of signs after exposure to their original diet. It is therefore strongly recommended to initiate an elimination trial using a novel protein or hydrolyzed peptides before contemplating more invasive diagnostic procedures. Owner compliance is notoriously an important limiting factor in elimination trials, and all necessary steps must be taken to ensure that the trial is carried out reliably Beside complete hematological and biochemical blood analysis, serum thyroxine concentration (particularly in cats > 7 years old), determination of feline PLI (fPLI, feline pancreatic lipase immunoreactivity) and abdominal ultrasound are usually selected to rule out chronic diseases affecting other organ systems. Abdominal radiographs may be indicated if a chronic intestinal obstruction is suspected (such as linear foreign body). Classically, radiographs are not very sensitive to rule out abdominal conditions such as chronic kidney disease, liver diseases or exocrine pancreatitis, and abdominal

Table 1. Clinical Signs Reported in 143 Cats with IBD.
(The details of the cited studies are listed at the end of this article.)

Variable	Michigan State Univ. 1992 14 cats	Iowa State Univ. 1992 26 cats	Animal Med. Ctr. 1994 60 cats	U. of Penn 1999 33 cats	Animal Med. Ctr. 2006 10 cats
Mean age in years (range)	6.8 (1-13)	6.9 (0.7-20)	9.5 (0.5–19)	7 (0.6–15)	9.7 (1.5–16)
Vomiting O: < once daily F: > once daily	10 (71%) O: 4 (28%) F: 6 (43%)	11 (42%)	46 (77%) O: 36 (60%) F: 10 (17%)	24 (33%)	4
Diarrhea LB: large bowel SB: small bowel M: mixed	7 (50%) SB: 5 (36%) LB: 2 (14%)	12 (46%) SB: 3 (11%) LB: 9 (35%)	21 (37%) SB: 2 (20%) LB: 7 (12%) M: 2 (3%)	16 (48%)	3
Inappetence/anorexia		11 (42%)	24 (40%)	6 (18%)	3
Lethargy	6 (43%)	NR	10 (17%)	3 (9%)	
Weight loss	10 (71%)	11 (42%)	38 (63%)	18 (55%)	6
BCS ≤ 3/9 (thin or cachectic)	NR	NR	30 (50%)	NR	5
BCS ≥ 4/9	NR	NR	30 (50%)	NR	5
Thick intestinal loops on physical exam (PE)	5 (36%)	NR	31 (52%)	NR	3
Large abdominal lymph nodes on PE	NR	NR	NR	NR	1

ultrasound is often preferable. In a retrospective study of 17 cats undergoing abdominal ultrasound, changes were noted in 13 (more than two thirds), and included poor intestinal wall layering, focal thickening, and hypoechoic and/or large mesenteric lymph nodes.

Abnormal laboratory results in cats with IBD may vary widely. They include anemia or hemoconcentration, leukocytosis with neutrophilia and left shift, eosinophilia, or leukopenia, hyper- or hypocholesterolemia, hypokalemia, hypoalbuminemia, and high alanine aminotransferase (ALT), aspartate aminotransferase (AST), or alkaline phosphatase (ALP) serum activity. Increases in serum liver enzyme concentrations could be due to increased intestinal permeability associated with inflammation, and presence of micro-organisms, inflammatory mediators and/or endotoxin in the portal blood. Alternatively, cholangiohepatitis (and pancreatitis) may occur more frequently in cats with IBD. The term "triaditis" was introduced 10 years ago, but has not gained universal acceptance due to a lack of additional evidence in the literature.

Once intestinal parasite infestation, fungal infection, adverse reaction to food, and extra-gastrointestinal illnesses have been systematically ruled out, two diseases remain on the list of differential diagnoses: IBD and gastrointestinal lymphoma. A recent study showed that cats affected with these two diseases share a very similar clinical presentation. Cats with GI lymphoma tended to be older with a mean age of 12.5 years (range 10–15 years) when compared with IBD cats (mean 9.7 years old, range 1.5-16). However, presenting complaint, clinical signs, and laboratory abnormalities were similar in both groups. Even ultrasound changes were not different. Therefore, obtaining mucosal biopsies is crucial to the diagnosis of one or the other disease. In that study, although endoscopy was deemed appropriate to deliver representative gastric biopsies for the diagnosis of gastric lymphoma, it was unreliable to diagnose small intestinal lymphoma when compared with the gold standard of full-thickness biopsies taken during exploratory laparotomy.

Endoscopic examination of the feline GI tract, although very helpful in many situations, suffers from several shortcomings. First, endoscopes only allow access to stomach and duodenum (possibly proximal jejunum) and colon. Even though biopsy of the ileum can sometimes be performed with the endoscope placed in the proximal colon, most of the jejunum cannot be explored. Second, lesions observed macroscopically during endoscopy do not correlate well with histopathology findings. Finally, the mucosal biopsies sampled endoscopically are superficial, and may show crush artifacts if instruments and technique are suboptimal.

It is notoriously difficult for pathologists to differentiate mild lymphoplasmacytic intestinal mucosal infiltration from normal mucosa on the basis of endoscopic biopsy samples. Adding to the confusion, some small cell lymphomas may have a histological appearance very similar to lymphoplasmacytic mucosal infiltration. In a revealing study, different board-certified pathologists delivered diverging interpretations when asked to look at the same biopsy samples. It is therefore very important that clinicians and pathologists have a chance to discuss difficult cases together. Both parties may gain significant information from such discussions to the final benefit of the patient.

Feline IBD is most commonly associated with lymphoplasmacytic enteritis and/or colitis with superficial infiltration. However eosinophilic enteritis and/or colitis have been reported occasionally. The eosinophilic infiltration typically reaches into the deeper layers of the intestinal wall, and the disease is associated with a less favorable prognosis.

THERAPY

Treatment is usually initiated once a diagnosis of histological diagnosis of IBD has been made. Empirical treatment can be considered in cats with suspect IBD that cannot undergo a full workup for financial or medical reasons

In addition to dietary treatment with a novel protein or hydrolyzed peptide diet, the mainstay of IBD treatment is immune suppression. Prednisone (or prednisolone) is administered at a dose of 4 mg/kg PO (once daily or in two divided daily doses) for 10 days. Then the dose is reduced by one half every 10 to 14 days. The final goal is to maintain the cat on the lowest effective dose of prednisone, or even to consider discontinuation of steroid treatment.

Other immune suppressive drugs used in cats include chlorambucil and cyclosporine. Both are second line agents that are used if adequately dosed steroid treatment only leads to partial remission, or in case of treatment failure. Chlorambucil, a nitrogen mustard derivative, is generally used alone or in combination with prednisone at a dosage of 2 mg P.O. per cat every other day (in cats $\geq$ 4 kg body weight) or every 3 days (in cats < 4 kg body weight) and then tapered to the lowest effective dose. CBC should be checked regularly for myelosuppression. Although there are no published reports of cyclosporine use in cats with IBD, the dose generally used is approx. 5 mg/kg once daily (25 mg/cat). A search for underlying infectious diseases such as toxoplasmosis, FeLV and FIV is recommended prior to use of immune suppressive agents.

Metronidazole, an antimicrobial agent with some immunomodulating properties, is also used to treat feline IBD. The recommended dosage is 10 to 15 mg/kg PO BID. The therapeutic range of metronidazole in cats is narrow, and caution is warranted with prolonged use of the drug. Side effects are mostly neurologic.

It has been demonstrated that cobalamine (vitamin B12) deficiency exists in a subset of cats with IBD. This can easily be confirmed by evaluation of serum cobalamine concentration. Vitamin B12 is involved in several important pathways of the intermediary metabolism. Deficient cats experience a delayed recovery or, worse, treatment failure after immune suppressive therapy. Cobalamine must be administered to these patients at a dosage of 250 µg SC for a 5-kg cat. The injections are given weekly for 6 weeks, then every other week for 6 weeks, finally at monthly intervals. Additionally, in one study, vitamin K malabsorption leading to abnormal PIVKA coagulation test results was detected in 11 of 19 cats with severe IBD, and 1 cat was noted to have bleeding tendencies. Vitamin K deficiency was attributed to intestinal malabsorption in these patients. Vitamin K1 supplementation may be beneficial in cats with severe IBD and abnormal absorptive function (1 to 5 mg/kg SC daily).

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FELINE PANCREATITIS – A CRITICAL APPRAISAL OF DIAGNOSIS AND MANAGEMENT

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Feline pancreatitis is an important and relatively common disorder that may be associated with high morbidity and occasional mortality. Acute (AP), recurrent acute, and chronic pancreatitis (CP) are all recognized as clinical entities. In a recent prospective study evaluating the prevalence and histopathologic characteristics of pancreatitis in cats, the prevalence of chronic pancreatitis was relatively high in 115 cats examined (67%), and chronic pancreatitis changes were relatively commonly found in apparently healthy cats. Of equal importance was the histologic finding of chronic pancreatitis in cats with no history or evidence of gastrointestinal disease, suggesting that the pancreas is highly sensitive to drugs, metabolic derangements or ischemia. A significant correlation was found between age and chronic pancreatitis in the cat. Several investigators have suggested that Siamese cats are more likely to develop pancreatitis compared with other breeds; however, our study failed to document a breed predilection. The clinical picture of pancreatitis in cats differs markedly from that in dogs. Cats develop chronic nonsuppurative pancreatitis (CP) more frequently than AP, and the two forms of pancreatitis cannot be distinguished from each other solely on the basis of history, physical examination findings, results of clinicopathologic testing, radiographic abnormalities, or ultrasonographic abnormalities. Vomiting and abdominal pain are far less commonly seen in cats with pancreatitis compared to dogs, and therapeutic recommendations for the cat are quite different to those in the dog with pancreatitis.

ETIOLOGY

The inciting cause of spontaneous feline pancreatitis in most cats is unknown, although pancreatic ischemia, trauma, organophosphate toxicity, and infectious agents including feline parvovirus, *Toxoplasma gondii*, feline herpesvirus I, *Eurytrema procyonis* (a fluke), feline infectious peritonitis (FIP), and, rarely, *Amphimerus pseudofelineus* have been implicated. Numerous drugs have been associated with causing pancreatitis in people and dogs; however, there is far less evidence for drug-associated pancreatitis in cats.

In contrast to people and dogs, obesity or increased body mass index (kg/m^2) has not been reported to be a risk factor for pancreatitis in cats.

The association of feline hepatic lipidosis or cholangitis and pancreatitis has been well documented. Pancreatitis is present in approximately 40% of cats with hepatic lipidosis and usually warrants a poorer prognosis when present. It is difficult to predict which disease occurs initially. Speculation is also increasing about the association between feline inflammatory bowel disease and pancreatitis.

CLINICAL PRESENTATION

The clinical presentation of cats with pancreatitis is vague and nonspecific. In a retrospective study of 40 cats with necropsy-confirmed pancreatitis, reported clinical signs were lethargy in 100% of the reported cases, anorexia in 97%, dehydration in 92%, hypothermia in 68%, vomiting in 35%, abdominal pain in 25%, palpable abdominal mass in 23%, dyspnea in 20%, ataxia, and diarrhea in 15%. In contrast, vomiting and abdominal pain are the most consistent clinical signs in dogs and in humans suffering from pancreatitis. Clinical signs associated with intestinal disease (IBD) or liver disease (hepatic lipidosis or cholangitis) may represent the sole reason for the animal to be presented for evaluation.

DIAGNOSIS

The complete blood count often shows mild and nonspecific changes, including a mild-to-moderate leukocytosis with or without toxic changes. The hematocrit can be increased (dehydration) or decreased (anemia of chronic disease). The serum biochemistry profile may reveal mild to moderate azotemia secondary to dehydration, or coexistent renal insufficiency. Increased liver enzyme activities reflect hepatic ischemia or concurrent lipidosis or cholangitis. Hyperbilirubinemia is more likely seen in cats due to the higher likelihood of obstruction of the pancreatic duct (pancreatic duct and common bile duct fuse to form a single duct in cats), or the presence of concurrent hepatic lipidosis or cholangitis. Hyperglycemia can also be seen secondary to diabetes mellitus or stress. Hypocalcemia secondary to saponification of fat and chelation with calcium can be seen, and decreased serum ionized calcium concentrations has been associated with a poor prognosis. Serum amylase and lipase activities are of no value in the diagnosis of feline pancreatitis. In addition, the relatively low sensitivity of increased serum feline trypsinogen-like immunoreactivity (fTLI) in cats with pancreatitis (30%–60%) has resulted in this test falling out of favor among veterinarians. In contrast, measurement of increased serum feline pancreatic lipase immunoreactivity (fPLI) has been demonstrated to be a far more sensitive test, particularly for detection of AP in cats, in which sensitivities approaching 100% have been documented. The fPLI is less sensitive in cats with mild pancreatitis, and additional studies are warranted to further evaluate the performance characteristics of this assay in cats with mild disease. Abdominal radiographs are relatively insensitive in cats with pancreatitis, and may show evidence of an increased density or diminished contrast and granularity in the right cranial abdomen. The angle between the pyloric antrum and proximal duodenum can be widened. Abdominal ultrasound is an extremely useful diagnostic tool, although the sensitivity of the procedure ranges from 50% to 80%, and is largely operator and equipment dependent. Ultrasonographic features of AP include an enlarged and irregular hypoechoic pancreas surrounded by a hyperechoic mesentery associated with focal peritonitis. Dilation of the cystic duct with scant amounts of abdominal effusion can be seen in cats with severe disease. Cats with CP may have evidence of a hyperechoic pancreas. The current "gold standard" for diagnosing pancreatitis is pancreatic biopsy for histologic evaluation. Peripancreatic fat necrosis is a typical finding in cats with pancreatitis, with variable amounts of acinar cell necrosis and inflammation. Chronic pancreatitis is characterized by interstitial fibrosis with acinar atrophy and lymphocyte infiltrates.

TREATMENT

The traditional therapeutic approach to cats with pancreatitis is largely supportive and symptomatic because an underlying cause of disease is rarely identified. Many cats with pancreatitis present with a history of anorexia, and fasting the cat for an additional 2 to 4 days to "rest" the pancreas will be of little to no clinical benefit, unless the cat is vomiting intractably or is nauseous. In addition, there is little clinical evidence to support excessive dietary fat restriction in cats with pancreatitis. Parenteral fluid and electrolyte replacement, analgesia, antiemetic therapy (when warranted), and appropriate nutritional support are the mainstays of therapy in the cat. Other therapeutic strategies such as fresh frozen plasma administration, antibiotic therapy, dopamine administration, corticosteroids, peritoneal dialysis, and surgery have been reported, although several of these strategies remain controversial.

Fluids and Electrolytes

The foundation of treatment for cats with severe acute necrotizing pancreatitis is similar to that in the dog with AP. These cats present with a more acute history of anorexia, vomiting, and weight loss, and many cats will be icteric due to extrahepatic bile duct obstruction. Maintenance of fluid and electrolyte balance is of paramount importance in these animals.

Antibiotics

Although controversial, antibiotic administration is best avoided unless the animal is febrile or exhibits toxic changes on the hemogram, or shows evidence of melena. Most cats with pancreatitis have a sterile pancreas and inappropriate antibiotic administration could result in anorexia, salivation, and vomiting. If indicated, one can administer enrofloxacin (2.5 mg/kg IV q 12 hr) and cefotaxime (25–50 mg/kg IV q 8 hr), as these drugs penetrate well into the pancreas.

Antiemetics

Antiemetic therapy is indicated if the vomiting is persistent or severe. There are a number of important differences between the neurotransmitter-receptor systems of the dog and cat. For example, apomorphine, a D2-dopamine receptor agonist, is a potent emetic agent in the dog but not the cat. This finding has an important implication, in that CRTZ D2-dopamine receptors are not so important in mediating humoral emesis in the cat, and that D2-dopamine receptor antagonists such as metoclopramide may not be as useful as other antiemetic agents in the cat. Alpha-2 antagonists might be more useful antiemetic agents than D2-dopamine antagonists in the cat. Finally, histamine and H1- and H2 histaminergic receptors have been demonstrated in the CRTZ of the dog, but not the cat. Histamine is a potent emetic agent in the dog, but cats seem resistant to its emetic effects. Metoclopramide is most effective when administered as a constant rate infusion at a dose of 1–2 mg/kg IV q 24 hours. This drug can be combined with a phenothiazine derivative such as chlorpromazine at a dose of 0.5 mg/kg IV or SQ q 6 to 8 hours. If the vomiting is not adequately controlled with metoclopramide and chlorpromazine, a serotonergic antagonist such as dolasetron at 0.5–1.0 mg/kg IV or SQ q 8 to 12 hours should be considered.

Analgesics

Pain control is an important aspect of supportive care for cats with pancreatitis, even if the cat is not showing overt signs of pain. Analgesic therapy can be provided using injectable opioids such as buprenorphine (0.005–0.01 mg/kg SQ or IV q 4–8 hours) or oxymorphone (0.05–0.1 mg/kg IM or SQ q 1–3 hours). A transdermal fentanyl patch (Duragesic, Janssen) applied to a clipped clean area of skin is a good way of providing a longer duration of analgesia (25 µg/hr patch q 5 days). Adequate fentanyl levels are not attained for between 6-48 hours after application, so another analgesic should be administered in the short term. Some cats with severe abdominal pain require constant-rate infusions of lidocaine (20 µg/kg per minute IV) or ketamine (2 to 20 µg/kg per minute or 0.1 to 1.2 mg/kg q 1hour IV) used with buprenorphine or other opioid drugs.

H2-Receptor Antagonists

Gastric mucosal protection with an H2 blocker (famotidine or ranitidine) is recommended in patients with acute pancreatitis where gastric mucosal viability is compromised. Ranitidine administered at 1–2 mg/kg IV or SQ q 12 hours is a good choice of H2 blocker, because the drug has in vitro prokinetic activity which could be beneficial if the animal has ileus or delayed gastric emptying in association with the pancreatitis and focal peritonitis.

Plasma

Severe pancreatitis is also associated with a marked consumption of plasma protease inhibitors as activated pancreatic proteases are cleared from the circulation. Saturation of available α_2-macroglobulins is rapidly followed by acute DIC, shock, and death. Although controversial, transfusion of fresh frozen plasma (20 mL/kg IV) or whole blood to replace α_2-macroglobulin may be life saving under these circumstances. In clinical trials in human patients with acute pancreatitis there was little evidence of any benefit of plasma administration. Nevertheless, many veterinarians feel that small animal patients with severe pancreatitis benefit from plasma administration as it serves as a colloidal agent, provides clotting factors, and provides protease inhibitors.

Colloids

Colloid support to enhance pancreatic perfusion can be supplied with hydroxyl starch or high molecular weight dextran (10–20 mL/kg/day IV).

Corticosteroids

Anti-inflammatory dosages of corticosteroids (2.5 mg per cat q 12 hours) have been given in cases of acute pancreatitis and necrotizing pancreatitis with no documented adverse effect. Anecdotally, the evidence for prednisolone administration appears positive, and controlled, randomized, blinded prospective clinical trails are warranted to further evaluate this therapeutic approach. Corticosteroid administration is not contra-indicated in cats with concurrent disorders such as IBD or cholangitis that are typically prednisolone-responsive.

Dopamine

The use of dopamine by constant rate infusion at 5 μg/kg/min has been shown to be beneficial in preventing exacerbation to severe hemorrhagic pancreatitis in a feline model of pancreatitis. This effect is probably mediated by ameliorating increases in microvascular permeability that could promote pancreatic edema. Unfortunately, this effect was only shown when dopamine was administered within 12 hours of initiating pancreatitis in these cats. Clinical trials evaluating dopamine in cats with spontaneous pancreatitis are warranted before this drug can be uniformly endorsed.

Pancreatic Enzyme Supplements and Somatostatin

Pancreatic enzyme supplements may decrease abdominal pain probably by feedback inhibition of endogenous pancreatic enzyme secretion. Similarly, somatostatin and its analogues inhibit pancreatic secretions, although clinical studies have failed to show any ameliorating effects of spontaneous pancreatitis in human beings. The author does not administer pancreatic enzyme supplements to cats with pancreatitis, unless the cat has concurrent exocrine pancreatic insufficiency.

Vitamin B12

A high proportion of cats with pancreatitis can have subnormal cobalamin (vitamin B12) concentrations. Supplemental parenteral cobalamin should be given when required at 250 μg per cat q weekly for 6 weeks, with reevaluation of cobalamin concentrations on a monthly basis. Vitamin B12 has a relatively short half-life in cats, and repeat administration of vitamin B12 is commonly required.

Novel Medical Approaches

Many other therapeutic strategies, such as the administration of trypsin-inhibitors (eg, trasylol), platelet activating factor inhibitors (lexipafant), antisecretory agents (ie anticholinergics, calcitonin, glucagon, somatostatin), or selenium have been evaluated in human patients with pancreatitis. With the exception of platelet activating factor inhibitors and selenium, none of these strategies have shown any beneficial effect at this point. The efficacy of selenium, which has also been shown to decrease mortality in dogs with pancreatitis in an uncontrolled study, needs to be evaluated in cats with pancreatitis.

Peritoneal Lavage

The theoretical benefits of peritoneal lavage (PL) for treatment of pancreatitis include removal of harmful substances released into the peritoneal cavity such as trypsin and kinins. A recent meta-analysis of eight prospective, randomized clinical trials in humans evaluating the use of continuous PL found no significant improvement in morbidity and mortality in patients with AP. Given the lack of efficacy of this treatment, the procedure is no longer recommended for use in humans with AP. To date, there are no studies specifically evaluating the use of PL as a therapy for dogs with naturally occurring AP. Given the potential risks (eg, peritonitis, hypovolemia, hypoalbuminemia), increased costs, and increased level of intensive care associated with PL, this therapeutic modality should be carefully considered before it is instituted.

DIETARY THERAPY

In contrast to dogs, there is little clinical evidence to support excessive dietary fat restriction in cats with pancreatitis. At the University of California, Davis VMTH, cats with pancreatitis that are anorectic, have lost significant body weight, or are diagnosed with concurrent hepatic lipidosis, *and are not vomiting intractably,* undergo esophagostomy tube placement for enteral feeding. Most of these cats do well on a complete and balanced commercial maintenance diet or a diet that is slightly fat restricted. Jejunostomy tube feeding or total parenteral nutrition can be used in cats that are vomiting despite the administration of antiemetic therapy. Surgical placement of jejunostomy tubes is preferred over percutaneous endoscopic placement. It is unnecessary to feed human liquid formulas and liquid veterinary products that frequently contain large amounts of fat. In addition, most human liquid enteral formulas are too low in protein, are free of taurine, and deficient in arginine for the maintenance of feline patients.

SURGICAL INTERVENTION

Direct comparisons between human studies and the few small studies that have been published in the veterinary literature should be interpreted with caution, because the findings are confounded by the differing terminology, diagnostic testing, surgical procedures, and postoperative management. Indications for surgical intervention in cats with pancreatitis include pancreatic infection (infected necrosis or pancreatic abscess), obstructive cholangitis with progressive hyperbilirubinemia, pancreatic neoplasia, and failure to respond favorably to medical management. Additional studies are warranted to identify more objective criteria for surgical intervention in dogs and cats.

Prognosis

Pancreatitis is an unpredictable disease of widely varying severity. Life-threatening signs accompanying acute fulminating pancreatitis are usually followed by death in spite of supportive measures, but some cats recover fully following an isolated severe episode. In other cases, relatively mild or moderate chronic or recurrent pancreatitis persists despite all therapy, and either the patient dies in an acute severe exacerbation of the disease or is euthanatized because of failure to recover and the expense of long-term supportive care. Cats with concurrent acute pancreatitis and hepatic lipidosis have a much poorer prognosis compared to cats with hepatic lipidosis alone.

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CRITICAL APPRAISAL OF INFECTIOUS DIARRHEA IN CATS

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Diarrhea in cats is one of the most common maladies facing the small animal practitioner and managers of feline shelters and catteries today. A recent survey of the Association of Shelter Veterinarians identified kitten diarrhea as one of the top two concerns of veterinarians treating shelter cats, second only to upper respiratory infections. Despite the significant clinical importance of diarrhea in cats, there is a paucity of veterinary literature providing specific information on the causes and diagnosis of this malady. Antibiotics are commonly administered injudiciously to diarrheic cats, with resolution of clinical signs often wrongly equated with eradication of a “putative” infectious pathogen. In addition, indiscriminate antibiotic therapy may even alter the commensal intestinal microflora, leading to an exacerbation of the animal’s diarrhea or development of antibiotic resistance. Knowledge of the most common infectious diseases of the gastrointestinal tract of cats is integral to formulating an appropriate diagnostic and therapeutic plan, and guiding the veterinarian where to turn when standard therapeutic recommendations fail.

Although diarrhea in cats can be associated with a number of different etiologies, infectious causes are believed to play an important role in many of these cases. Potential causes of bacterial-associated diarrhea in cats include enteropathogens such as *Salmonella* spp, *Campylobacter* spp, *Clostridium perfringens*, and *Clostridium difficile*.[12] Intestinal endoparasites such as *Toxocara cati, Toxascaris leonina,* and *Ancylostoma* spp are occasionally associated with diarrhea in cats, whereas intestinal protozoa such as *Giardia* spp, *Tritrichomonas foetus*, *Cryptosporidium* spp, and *Isospora felis* are more commonly incriminated. Of particular concern, several of these enteropathogens have been clearly implicated as zoonotic agents, including *Salmonella* spp, *Campylobacter* spp, *Toxocara cati*, *Giardia* spp, and *Cryptosporidium* spp, underscoring the importance of accurately diagnosing these pathogens in affected cats. Enteric viruses, including feline parvovirus, rotavirus and astrovirus have also been isolated in some cases, although the pathogenicity of the latter viruses in feline diarrhea is poorly understood.

INTESTINAL ENDOPARASITES

The diagnosis of gastrointestinal parasites in cats is an integral component of small animal practice; however, there is little uniformity in the application of diagnostic techniques and suboptimal attention to proper identification of parasites in many instances. The guidelines below should be followed to maximize the diagnostic yield of fecal examinations.

Examine Fresh Fecal Specimens

Fecal flotations should be performed on fresh fecal specimens (< 1 hour old) to ensure that eggs, oocysts, and larvae do not develop beyond their diagnostic stage. Fresh fecal specimens can be refrigerated within 1 hour of collection for up to 72 hours to facilitate preservation of eggs, oocysts, and cysts if immediate examination cannot be performed. Specimens fixed in formalin are suitable for concentration techniques, acid fast stains, and immunoassays. Survival of trichomonads can be extended by simply adding saline to the fecal specimen (3 mL of 0.9% saline per 2 grams feces) to prevent desiccation.

Perform Direct Wet Smears Routinely

Direct wet smears are indicated for recovery of trophozoites of *Giardia* and *Tritrichomonas foetus*. They must be done with saline and performed using fresh feces (body temperature, < 1 hour old). Trophozoites in older specimens will lose their motility and degenerate, becoming unrecognizable. The sensitivity of direct wet smear examination for diagnosis of trichomoniasis is relatively low in cats with spontaneous disease (14%). In addition, *T. foetus* can be difficult to distinguish from non-pathogenic intestinal trichomonads such as *Pentatrichomonas hominis* and *Giardia* using light microscopy. *Giardia* trophozoites have a concave ventral disc and motility mimicking a “falling leaf.” In contrast, *T. foetus* is spindle shaped, has an undulating membrane that courses the entire length of the body, and moves in a more irregular and jerky fashion.

Perform Centrifugation Fecal Flotations

Fecal flotations are excellent for recovering common nematode ova, oocysts of coccidia (including *Cryptosporidium* spp), and *Giardia* cysts. The most important considerations for fecal flotations include: 1) choice of flotation solution and its specific gravity, 2) selection of standing versus centrifugal flotation, and 3) transfer of the meniscus.

Flotation Solutions

The flotation solution must have a specific gravity high enough to float most common parasite ova and low enough to avoid distortion of protozoal cysts. Three solutions in common use are zinc sulfate (s.g. 1.18 to 1.2); Sheather’s sugar (s.g. 1.27); and sodium nitrate (s.g. 1.2). Sodium chloride is an unacceptable flotation medium, even when used with centrifugation, as it will not float *Trichuris* ova. Aqueous zinc sulfate ($ZnSO_4$) with a specific gravity of 1.18 to 1.2 has been widely recommended because it will float cysts, oocysts, and most helminth eggs with a minimum of distortion and fecal debris. It is important to note that zinc sulfate at this concentration will not recover spirurids (*Physaloptera*) and *Taenia* spp, whose specific gravities are 1.23 and 1.22, respectively.

Centrifugation versus Gravity (Standing) Flotation

Gravitational (standing) flotation is the mainstay of veterinary practitioners and some reference laboratories.

The use of this method has been perpetuated by the advent of commercial devices (eg, Ovassay®, Fecalyzer®, Ovatector®) which allow the collection and processing of specimens with a minimum of handling by the client and technician. Flotation with centrifugation is considerably more efficient than standing flotations, which may not detect parasite stages shed in low numbers. Quantitative comparisons have shown that egg counts achieved using flotation with centrifugation were 2.4 to 6.0 times higher compared with standing flotation.

Meniscus Transfer

Once the flotation procedure is complete, the meniscus containing the parasite stages should be transferred by coverglass. The meniscus should be transferred by lifting the coverslip directly off the fluid surface after 10 minutes and placing it on a slide. Meniscus transfer using a loop or glass rod is the poorest method of meniscus transfer and reduces the sensitivity of any flotation technique because only a small portion of the parasites recovered are actually transferred to the slide for examination.

Procedure for Centrifugation Flotation (Centrifuge with Free-swinging Buckets)

1. Prepare a fecal emulsion using 2–5 grams of feces and 30 mL of flotation solution.
2. Strain the emulsion through a tea strainer or cheesecloth into a 15-mL conical centrifuge tube.
3. Fill the tube with flotation medium to create a meniscus.
4. Place a coverslip on top of the tube.
5. Create a balance tube of equal weight, containing another sample or water.
6. Centrifuge the tubes for 5 minutes at approximately 1,200 rpm (280 x g).
7. Carefully remove the coverslips from the tubes after 10 min and place them on a slide.
8. Examine the slide within 10 minutes. Examine entire coverslip at 10X. Use 40X to confirm identification by visualizing internal structures and measuring the organism.

If the centrifuge is a **fixed-angle type**, one should fill the centrifuge tube with flotation medium to within one inch from the top of the tube. After centrifugation, the meniscus can be raised to the top of the tube by carefully adding more flotation medium with a pipette down the side of the tube after the final spin. A coverslip is then placed on top of the tube for 10 minutes before transferring it to a glass slide for examination.

GIARDIA Spp

Giardia infections in adult cats are often subclinical or associated with a transient softening of the stool early in the infection; however, acute diarrhea tends to occur in kittens shortly after infection. Feces are often malodorous and pale, and may contain mucus.

Diagnosis

The diagnosis of *Giardia* infection traditionally has depended on microscopic identification of trophozoites or cysts in feces from affected animals. However, microscopic diagnosis of *Giardia* infection can be difficult, because cysts may be shed intermittently and because cysts are so delicate. Many artifacts (grass pollen, yeast, etc.) mimic to varying degrees the morphology of *Giardia* cysts, and care must be exercised in differentiating these from *Giardia*. The need for accurate identification of these parasites in diarrheic cats is important when one considers that the organism is a zoonosis, and that failure to detect these parasites in diarrheic animals often leads to injudicious antibiotic therapy, which can exacerbate the diarrhea.

Many veterinarians and reference laboratories have resorted to using ELISA tests that rely upon detection of *Giardia* cyst wall protein I (GCWP 1). The ELISA tests are advantageous because they are generally easy to perform and results are easy to interpret. In addition, the test does not rely upon morphologic identification of cysts or oocysts via microscopy, thus saving technician time and potentially avoiding false negative interpretations. The EIA tests can also detect GCWP 1 in the absence of detectable cysts. Recently, a novel SNAP® *Giardia* Test Kit (IDEXX Laboratories) for detection of GCWP 1 in canine and feline feces was released. The SNAP® *Giardia* Test is a rapid in-house enzyme immunoassay that can be performed on fresh feces, previously frozen feces, or feces stored at 2–7°C for up to 7 days. This test represents the first commercially available EIA designed specifically for dogs and cats, and has the added advantages of simplicity, rapid availability of results (8 minutes following mixing of the conjugate solution with feces), and low cost. The performance characteristics of this test have been evaluated in cats, and the test was both highly sensitive and specific (Table 1). Of equal importance, parallel testing of fecal specimens with both fecal centrifugation flotation and the SNAP *Giardia* test increased the sensitivity for detection of *Giardia* spp. to 97.8%.

Direct immunofluorescence (DIF) is often the standard against which other tests for *Giardia* are measured. The Merifluor® *Cryptosporidium/Giardia* assay (Meridian Diagnostics) uses a fluorescein isothicyanate (FITC)–labeled monoclonal antibody directed against cell wall antigen of *Giardia* cysts (not trophozoites) in the feces. A positive result is indicated by apple green fluorescence of the cyst. Morphologic identification is necessary for this technique. The test has been shown to have excellent specificity and sensitivity in humans,[34] although it requires a fluorescent microscope which is typically available in large reference laboratories or universities. Specimens sent to commercial laboratories for DIF should be fixed in 10% buffered formalin. Meridian's DIF combines the *Giardia*-specific and *Cryptosporidium parvum*-specific antibodies in one reagent, so specimens can be examined for both parasites with a single test.

Table 1. Performance Characteristics of Enzyme Immunoassays and Fecal Flotation for Diagnosis of *Giardia* in 344 Cats

	Sensitivity (%)	**Specificity (%)**	**False Negatives**	**False Positives**
Flotation	85.3	99.7	5	1
Immunocard STAT!	72.7	99	9	3
XpecT Giardia/Crypto	79.4	99	7	3
SNAP Giardia ELISA	85.3	100	5	0
ProSpecT Giardia Microplate ELISA	91.2	99.4	3	2

Therapy

Metronidazole was shown to be highly effective and safe when given at 25 mg/kg PO q12h for 7 days to cats with experimental infections,[35] although it is less effective in dogs with eradication of the organism occurring in 67% of treated dogs. Albendazole is also relatively effective when dosed at 25 mg/kg BID for 5 days; however, the drug has been associated with pancytopenia and is teratogenic. A recent trial evaluating the efficacy of fenbendazole in cats co-infected with *Cryptosporidium parvum* revealed that the drug was safe; however, it was relatively ineffective (50%) in cats co-infected with *Cryptosporidium*.[36] Fenbendazole is the author's first drug of choice for treating infected kittens. Drontal Plus was shown to be relatively safe and effective in experimentally infected kittens when given at twice the recommended dose.[37] The dose of febantel administered was 56.5 mg/kg q12 hours for 5 days. Prevention of reinfection by decontaminating the environment and bathing the animal to clean cysts from the coat are important strategies in the management of infected animals.

CRYPTOSPORIDIUM

Cryptosporidium spp infection of kittens and healthy or immunosuppressed cats can cause a spectrum of severity of disease, ranging from a non-clinical carrier state to mild, transient diarrhea, cholera-like illness, or prolonged severe life-threatening malabsorption syndrome. Infection with *C. parvum* in one cat was associated with chronic diarrhea, anorexia, weight loss, and, histologically, a lymphocytic-plasmacytic intestinal infiltrate similar to that seen in inflammatory bowel disease.

The laboratory detection of *Cryptosporidium* spp in naturally exposed cats with diarrhea is difficult, mainly because the organism is small (mean size, 4.6 X 4.0 μm) and therefore difficult to detect via light microscopy, and because fecal shedding may be intermittent. Current laboratory methods for detection of *Cryptosporidium* oocysts in fecal specimens include light microscopic examination of fecal smears stained with Giemsa stain, modified Ziehl-Neelsen acid-fast stain, or modified Kinyoun acid-fast stain, or use of an immunofluorescence detection procedure. Immunofluorescence detection procedures are more sensitive and specific than acid-fast stains, and are generally the method of choice for morphologic diagnosis of cryptosporidiosis in humans. Although several diagnostic tests for cryptosporidiosis have come into widespread general use, there is little data in the veterinary literature that compare different methods of diagnosis in animals, and no single procedure has been universally adopted.

Therapy

Eradication of this parasite has proven difficult, and many putatively effective drugs are either toxic or ineffective. The aminoglycoside, paramomycin, is potentially nephrotoxic and ototoxic, and should not be used in animals with compromised renal function. A recent prospective blinded study completed by the author failed to show any benefit for tylosin in naturally infected kittens (Marks, unpublished observation). Azithromycin is used in humans for management of Cryptosporidiosis, and appears safe in dogs and cats when administered at a dosage of 7 to 10 mg/kg BID for 7 days; however, its efficacy is unknown.

TRITRICHOMONAS FOETUS

Tritrichomonas foetus, the primary causative agent of bovine trichomoniasis, has recently been recognized as a protozoal pathogen in cats. Infected cats are generally young, but have ranged in age from 3 months to 13 years (median 9 months). The prevalence of *T. foetus* infection at an international cat show was found to be 31% (36 out of 117 cats), with 28 out of 89 catteries affected. Co-infection by *T. foetus* and *Giardia* was common and was documented in 12% of cats. Misdiagnosis of *Giardia* is common in cats having *T. foetus* infection, and may explain why cats diagnosed with apparent *Giardia* infection do not respond to appropriate therapy.

Clinical signs of infection are characterized by a chronic or recurrent large intestinal diarrhea with increased mucous, tenesmus, occasional hematochezia, and increased frequency. The anus is frequently red, swollen, and painful, and fecal incontinence is not uncommon. Most cats are usually bright, alert, and responsive, and in good body condition with a normal appetite. *Tritrichomonas foetus* can also be cultured from the feces of asymptomatic cats, many of whom will not develop diarrhea. Consideration should be given to coexisting enteric infections in cats diagnosed with *T. foetus*. Studies of experimental feline infection showed that cats coinfected with *Cryptosporidium* spp had more severe diarrhea and increased shedding of *T. foetus* organisms. A fecal flotation and fecal ELISA or IFA for *Giardia* should be performed in cats infected with *T. foetus* because of the high incidence of co-infection with *T. foetus* and *Giardia* in cats.

Diagnosis

1) Multiple direct wet preparations on diarrheic fecal specimens

Direct fecal smears are performed to evaluate for the presence of *Tritrichomonas foetus* trophozoites. The sensitivity of direct fecal smear examination for diagnosis of *T. foetus* is relatively low in cats with spontaneous disease (14%). *T. foetus* can be distinguished from *Giardia* based on morphology and motility. *Giardia* trophozoites have a concave ventral disc and motility mimicking a falling leaf, whereas trichomonads are spindle-shaped, have an undulating membrane that courses the entire length of the body, and move in a more irregular and jerky fashion. *T. foetus* does not have a cyst stage, underscoring the limitations of fecal flotation for diagnosing this organism.

2) Fecal cultures performed with an InPouch TF kit

A commercially-available system marketed for diagnosis of *T. foetus* infection in cattle (InPouch TF, Biomed Diagnostics) is more sensitive than the direct wet preparation. Approximately 0.05 grams (less than a peppercorn) of freshly voided feces can be placed in the InPouch for culture, or alternatively, a saline-moistened cotton-tipped swab can be placed in the rectum and then gently agitated in the InPouch for culture. The InPouch should be incubated at 37°C or room temperature in an upright position in the dark, and examined q 48 hours for up to 10 days for motile trophozoites using a 20X or 40X objective. The media in the InPouch apparently does not support the growth of *Giardia* or *Pentatrichomonas hominis*.

3) Single tube nested PCR of DNA extracted from feces

A sensitive and specific single-tube nested PCR from feline feces has been described.[45] The PCR test is more sensitive than fecal culture and tested positive in 55% of cultures that were negative for *T. foetus*, even when feces were normal.

4) Colonic mucosal biopsy

Colonic mucosal biopsies are not usually necessary to diagnose *T. foetus* infections in cats, and the procedure is typically performed when the above-mentioned diagnostic tests are negative or appropriate medical therapy does not result in resolution of clinical signs. Histopathologic changes in colonic mucosal biopsies from infected cats have predominantly consisted of a lymphocytic and plasmacytic infiltrate with a significant neutrophilic component. The intestinal epithelium is frequently attenuated, and immunohistochemistry can be utilized to detect the trichomonads on the surface epithelium and within crypts.

Therapy

Ronidazole, a nitroimidazole that has been used for the prevention and treatment of histomoniasis in turkeys, and the treatment of trichomoniasis in pigeons, is the drug of choice for treatment of *T. foetus* in cats. The drug is available from a variety of compounding pharmacies in the US, including RoadRunner in Phoenix, AZ, and Westlab Pharmacy in Gainesville, FL. The currently recommended dose of ronidazole is 30 mg/kg q 12 hours for 10 days. Caution should be heeded in using ronidazole that contains various fillers, amino acids, vitamins, etc., as these products have not been scrutinized in cats to date. Neurological adverse effects have been documented in cats given ronidazole at 40 mg/kg BID, hence the recommendation for the lower dose. The adverse effects (hyperasthesia, ataxia, weakness, and anorexia) can take up to 4 weeks to fully resolve following discontinuation of the drug. There are several other nitroimidazole drugs that are currently being evaluated for their efficacy in cats, including tinidazole and ornidazole; however, these drugs do not appear to be superior to ronidazole. Interestingly, metronidazole, another nitroimidazole with a very similar chemical structure to ronidazole, has been demonstrated to have *in vitro* efficacy against ronidazole in the author's laboratory; however, the drug is not effective *in vivo*.

Long-term follow-up of these cats (clinical signs, fecal cultures, and PCR) has revealed re-infections in a small number of cats. Some of these cats may in fact have had persistent infections, underscoring the importance of performing fecal cultures and/or PCR at the end of ronidazole administration to ensure successful eradication of the organism. Cats can have resolution of clinical signs despite showing evidence of infection on fecal culture or fecal PCR.

Environmental Control

There are no studies evaluating the natural transmission of *T. foetus* in cats, or the likelihood of transmission of the organism amongst cats in a multicat household. The mode of transmission is most likely the fecal-oral route or via contamination of water or food. Litter boxes should be cleaned on a consistent basis, and cages or litter boxes can be disinfected with quaternary ammonium compounds (eg, Roccal, Maxxon). The trophozoites are relatively labile, and should be easily killed with most disinfectants.

Public Health Considerations

To date, only a single case of human infection with *T. foetus* has been published in the literature.[49] The infection presented as epididymitis and meningoencephalitis following immunosuppression and peripheral blood stem cell transplantation. The paucity of documented zoonotic cases might be a reflection of the poor host specificity of *T. foetus*, or the need for certain strains to exist in a severely immunocompromised host. Nevertheless, because of the close association between infected cats and their human companions, the potential for zoonotic transmission should be considered.

ENTEROPATHOGENIC BACTERIA

Veterinarians are faced with a quandary when attempting to diagnose cats with suspected bacterial-associated diarrhea because the incidence of bacterial diarrhea is poorly documented and extremely variable, and putative infectious enteropathogens can commonly be isolated from healthy cats as well. It is plausible that co-factors are required to enhance the pathogenicity of infectious agents, or that species or strain differences account for the difference in clinical outcome. The latter point is particularly relevant given the author's recent findings in a clinical study in which *Campylobacter* spp were isolated from fecal specimens of 7/62 (11%) diarrheic adult cats, and from fecal specimens of 11/51 (20%) nondiarrheic adult cats.

CLOSTRIDIUM PERFRINGENS

Clostridium perfringens is an anaerobic, spore-forming, gram-positive bacillus that has been associated with outbreaks of acute, often severe diarrhea in humans, horses, dogs, and cats. The elaboration of four major toxins (α, β, ι, and ε) is the basis for typing the organism into five toxigenic phenotypes, A-E. Each type may also express a subset of at least 10 other established toxins, including *C. perfringens* enterotoxin (CPE), a well-characterized virulence factor whose production is co-regulated with sporulation. Cats with *C. perfringens*-associated diarrhea frequently exhibit large-bowel diarrhea characterized by increased frequency of bowel movements with tenesmus, fecal mucus and hematochezia; however, clinical signs of enteritis or enterocolitis are also commonly seen. The incidence of *C. perfringens*–associated diarrhea appears to be less common in cats compared to dogs, with approximately 14% of diarrheic cats testing positive for the enterotoxin via ELISA compared with approximately 30% of diarrheic dogs (Marks, unpublished observation).

Diagnosis

Current diagnosis of *C. perfringens*–associated diarrhea in the cat is made based on detection of CPE in fecal specimens in conjunction with clinical signs of disease. The value of quantitative fecal culture and fecal spore counts have been shown to be of poor diagnostic value, as the organism is isolated from more than 80% of healthy cats and there is no correlation between spore counts and detection of enterotoxin. There is only one commercially available ELISA kit (Techlab) for detection of CPE in fecal specimens; however, the performance characteristics of this assay have not been validated in the cat to date.

Therapy

Antibiotics that have been recommended for the treatment of *C. perfringens*–associated diarrhea include ampicillin (22 mg/kg TID), metronidazole (10 mg/kg BID), and tylosin (15 mg/kg BID). Tetracycline use should be avoided due to the high incidence of tetracycline resistance.

CLOSTRIDIUM DIFFICILE

Clostridium difficile is a gram-positive, anaerobic spore-forming bacillus, and is the major cause of antibiotic-associated pseudomembranous colitis in human patients. *Clostridium difficile* has also been associated with diarrhea and enterocolitis in foals and adult horses, as well as diarrhea in dogs and cats. *C. difficile*–associated diarrhea is less common in cats, and a recent study documented an incidence of 5% in diarrheic cats (Marks, unpublished observation). Two toxins, toxin A and toxin B, are thought to be primarily responsible for disease associated with the organism, although other toxins may also play a role.

Diagnosis

Current diagnosis of C. *difficile*–associated diarrhea is primarily made based upon detection of toxin A or toxin B in fecal specimens via ELISA. Isolation of the organism alone is not sufficient for diagnosis due to the presence of nontoxigenic strains. In addition, previous studies have reported no significant difference in the isolation of *C. difficile* from diarrheic and non-diarrheic dogs, although animals that are toxin positive are invariably culture positive.

Therapy

Metronidazole (10 mg/kg BID for approximately 7 days) administration is the therapy of choice for cats with suspected *C. difficile*-associated diarrhea. Although metronidazole-resistant *C. difficile* isolates obtained from foals and adult horses have been reported, the author is unaware of any documented cases of resistance in the cat. The second drug of choice in humans and occasionally in horses is vancomycin; however, it is used only in nonresponsive cases or when metronidazole-resistant strains have been demonstrated.

CAMPYLOBACTER

Campylobacter spp are small (0.2 to 0.5 μm x 0.5 to 5 μm), microaerophilic, gram-negative, curved rods that are members of the bacterial family Campylobacteracea. It has recently been shown that some selective media can have an inhibitory effect on a number of *Campylobacter* spp, resulting in more sensitive species, such as *C. upsaliensis* or other catalase-negative or weakly-positive species being missed. *Campylobacter* species that have been implicated in feline intestinal disease include *C. jejuni*, *C. coli*, *C. helveticus*, and *C. upsaliensis*. Other enteric pathogens, such as parvovirus, *Giardia*, or *Salmonella* may play a synergistic role. The isolation of *Campylobacter* spp from a diarrheic animal does not necessarily implicate *Campylobacter* as a cause of the diarrhea. A recent study in the author's laboratory documented a significantly higher incidence of *Campylobacter* spp in healthy, non-diarrheic cats (20%) versus diarrheic cats (11%) (Marks, unpublished observation).

Diagnosis

Campylobacter-like organisms (CLOs) can be identified by examining stained smears (gram stain or Romanovsky-type stain) of fresh feces from the patient. The organism's characteristic morphology (slender, curved rods with an "S" shape or sea gull-shaped appearance) allows it to be identified relatively easily. The major limitation of direct examinations is that the procedure fails to differentiate between *Campylobacter* spp or between related organisms including *Helicobacter* spp and *Anaerobiospirillium* spp. In addition, identification of CLOs is not sufficient to warrant a diagnosis of *Campylobacter*-associated diarrhea, as many healthy cats can harbor CLOs in their intestinal tract.

For optimal recovery of *Campylobacter* spp, feces or swabs of feces should be fresh or refrigerated at 4°C and should be immediately placed into anaerobic transport medium before refrigeration. For isolation, the use of a formulated selective medium containing antimicrobial agents (eg, Campy-CVA containing cefoperazone, vancomycin, and amphotericin B) gives better recovery than other direct-plating selective media. Microaerophilic incubation conditions should be maintained, and the plates should be incubated at 37°C, or at 42°C, when isolation of *C. jejuni* and *C. coli* from feces is attempted. Suspect colonies should be gram-stained and subcultured to 5% SBA. Biochemical tests are then performed to speciate all *Campylobacter*-like organisms isolated. The use of selective medium containing cefoperazone should be used when attempting to isolate *C. upsaliensis*, as the organism is more resistant to cefoperazone than to cephalothin. Characterization of *Campylobacter* infections or mixed infections with *Helicobacter* and *Campylobacter* spp is best accomplished utilizing molecular structure-based diagnostics, employing genus- and species-specific PCR, RFLP analysis, and 16S rRNA sequence analysis.

Therapy

Although diarrhea produced by *Campylobacter* organisms is usually self-limiting, the zoonotic potential of the organism often necessitates medical therapy. It is now recognized that *Campylobacter* are a leading cause of enteric disease in people and that diarrheic and nondiarrheic animals can serve as sources of infection for humans. The drugs of choice are the macrolides (erythromycin at 10 to 15 mg/kg TID) or quinolones (enrofloxacin at 5 mg/kg BID). However, due to the high rate of mutational resistance campylobacters have to the quinolones, a resistance that sometimes occurs while animals are being treated, quinolones are not the drug of choice. Erythromycin is the drug of choice, despite the associated gastrointestinal side effects. The duration of excretion in infected cats can be as long as 4 months and infected animals should be quarantined away from children during this period.

SALMONELLA

Salmonella are primarily motile, non-spore-forming, gram-negative aerobic bacilli of the family Enterobacteriaceae. There are currently over 2000 described serotypes of *Salmonella* that have been associated with both human and animal disease. *Salmonella* spp are one of the most common causes of human food-borne disease, with an estimated 1.4 million cases occurring annually in the United States. Clinical salmonellosis in cats is rare, although prevalence is higher in puppies and kennel populations. Isolation of *Salmonella* spp from adult dogs ranges from 0 to 2% in nondiarrheic animals, and from 0 to 1% in diarrheic dogs. The isolation rates are similar in nondiarrheic and diarrheic cats.

Clinical Signs

Signs of clinical salmonellosis in cats include fever, anorexia, diarrhea (which may be bloody), vomiting, weight and loss. Most *Salmonella*-infected cats are asymptomatic, although some animals may manifest clinical signs of sepsis.

Diagnosis

The traditional diagnosis of salmonellosis is made based on isolation of the organism in conjunction with clinical signs and assessment of potential risk factors such as hospitalization, age, environmental exposure, and antibiotic administration. However, isolation of *Salmonella* is not necessarily indicative of involvement in disease, as similar isolation rates can be detected in healthy nondiarrheic animals. Hematologic abnormalities are variable, and include a nonregenerative anemia, lymphopenia, thrombocytopenia, and neutropenia with a left shift. Toxic neutrophils are found in animals with systemic disease and endotoxemia, findings similar to those documented with canine parvovirus. Fresh fecal specimens should be placed onto one or more selective media, including MacConkey agar, XLD agar, and brilliant green agar. For enrichment, selenite F, tetrathionate, or gram-negative broth (GN) is recommended.

Therapy

Intravenous fluid therapy is recommended depending on the severity of the diarrhea. Antibiotic therapy is typically indicated for animals with concurrent signs of systemic infection, or histories of immunosuppression. Antibiotics reported to be effective against *Salmonella* include fluoroquinolones, chloramphenicol, trimethoprim-sulfonamide, and amoxicillin.

VIRAL ENTEROPATHIES

Feline viral enteritis is usually diagnosed in younger unvaccinated animals. The animal's signalment, history, clinical signs, and hematologic findings are important in ranking a viral etiology as a likely cause of the animal's diarrhea.

Feline Parvoviral Enteritis

Feline parvoviral enteritis (feline panleukopenia) is caused by a parvovirus distinct from CVP-2b, although this strain can infect cats and cause disease. Feline parvovirus has become an uncommon disease because of routine vaccination; however, outbreaks are occasionally seen in unvaccinated animals, particularly ferrel populations and catteries. The clinical signs are similar to those described for dogs with parvoviral enteritis.

Diagnosis

Diagnosis is based on the history, physical examination findings, results of a hemogram (neutropenia), and fecal ELISA. The ELISA test used to detect canine parvovirus has been reported to cross-react with feline parvovirus.

Treatment

Treatment is supportive and similar to other severe, acute infectious enteropathies. Intravenous fluid and electrolyte therapy is indicated, with particular attention given to potassium repletion. Dextrose solution (2.5–5%) is added to the IV fluids if the animal is hypoglycemic or at rate (eg, septic shock). Plasma or colloids (Dextran 70 or Hetastarch) are indicated if the serum albumin concentration drops below 2.0 g/dL). Antibiotics are administered to febrile or severely neutropenic cats. If the animal is neutropenic, but afebrile, the administration of a first-generation cephalosporin is reasonable. Cats in septic shock should be treated with a broad-spectrum aerobic and anaerobic antibiotic (eg, ampicillin plus amikacin). Human granulocyte colony-stimulating factor (G-CSF) at 5 µg/kg q 24 hours has been used to increase neutrophil numbers, but may not influence patient outcome. Antiemetics such as prochlorperazine, metoclopramide, or dolasetron (0.5–1 mg/kg q 12–24 hours), are indicated if the vomiting is intractable. Metoclopramide is most effective when administered as a constant rate infusion at a dose of 1 mg/kg/24 hours. Gastric protectants including H2-receptor antagonists and sucralfate are indicated if there is evidence of secondary esophagitis. Broad-spectrum anthelminthics to treat concurrent intestinal parasites should be administered when the cat is no longer vomiting. Most cats can be gradually weaned onto a commercially available highly digestible diet; however, the presence of intractable vomiting might warrant the administration of total parenteral nutrition.

References are available from the author upon request.

TREATMENT OF ACUTE AND CHRONIC PANCREATITIS

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Rational treatment of pancreatitis requires an understanding of the pathogenesis of the disease and shall thus be discussed briefly:

According to a generally accepted pathogenic principle pancreatic acinar cells ultimately respond in a common fashion to a variety of harmful stimuli, leading to inappropriate intracellular activation of trypsin, and subsequently activation of other digestive zymogens. These activated digestive enzymes cause local changes, such as inflammation, hemorrhage, acinar cell necrosis, and peripancreatic fat necrosis. Pancreatitis, when severe, is also associated with a variety of systemic complications such as systemic inflammatory changes, systemic vasodilatation leading to hypotension, pulmonary edema, disseminated intravascular coagulation, central neurologic deficits, respiratory failure, renal failure, and multiorgan failure. Traditionally, it was hypothesized that these changes, similarly to local changes are caused by prematurely activated pancreatic enzymes. However, more recently, cytokines are believed to play a more important role in the progression of pancreatitis and the development of these systemic complications.

Several diseases and risk factors have been associated with pancreatitis. Traumatic pancreatitis (due to road traffic accidents in both dogs and cats or falling from heights in cats) has been reported. Surgical trauma can cause pancreatitis but many human patients that undergo surgery of organs distant from the pancreas have also been shown to be at an increased risk for pancreatitis suggesting that hypoperfusion of the exocrine pancreas during anesthesia may be of bigger concern than surgical handling of the organ itself. Infectious agents have been shown to cause feline pancreatitis, with the strongest causal relationship for *Toxoplasma gondii*, and rare cases of Amphimerus pseudofelineus infestation in cats. Recently, *Babesia canis* has been reported to be associated with pancreatitis in dogs. Weaker evidence has been presented for feline panleukopenia virus infections in kittens and infections with feline herpesvirus I and feline infectious peritonitis virus. Two cases of feline pancreatitis after topical use of fenthion, an organophosphate cholinesterase inhibitor, have been reported. Many other pharmaceutical compounds have been implicated in causing pancreatitis in human beings and dogs, but no cases have been reported in cats. Cholangitis and cholangiohepatitis may coexist in patients with pancreatitis, but there is no evidence that they play a causative role. Finally, more than 90% of all cases of canine or feline pancreatitis are idiopathic.

THERAPY

Treatment of the Cause

Whenever possible the inciting cause should be removed. However, as indicated above this may be difficult to accomplish as most cases of canine and feline pancreatitis are idiopathic. A serum chemistry profile should be performed to rule out hypertriglyeridemia and/or hypercalcemia. Exposure to unnecessary drugs, especially those implicated in causing pancreatitis in dogs, cats, or other species, should be avoided. Thus, first, a careful, drug history should be taken. Then, the clinician should determine whether treatment is needed. For example, a patient that is treated with an anticonvulsant medication probably should be maintained on some anticonvulsant therapy, but, if being treated with potassium bromide and/or phenobarbital should be changed to another anticonvulsant medication.

Supportive Care

Aggressive fluid therapy is the mainstay of supportive therapy. Fluid, electrolyte, and acid-base imbalances need to be assessed, and corrected as early as possible. This is especially important since systemic complications are associated with a worse outcome and many of the systemic complications, once established, are difficult to treat.

Alimentation

The traditional recommendation for any patient with pancreatitis is to give nothing per os for three to four days. This recommendation may be justified in patients that vomit relentlessly. However, there is little evidence to justify this strategy in patients that do not.

The issue is complicated further in cats by the fact that cats with pancreatitis often develop hepatic lipidosis. Preferred routes of alimentation are a jejunostomy tube or total parenteral nutrition. However, these strategies are impractical in many cases and a gastrostomy tube or a nasogastric tube are acceptable alternatives if a patient does not vomit. There is good evidence in human patients with pancreatitis that alimentation is crucial to counterbalance the catabolic effects of pancreatitis and a nasogastric tube has been shown to be quite effective in humans with pancreatitis. However, regardless of the mode of alimentation, a diet low in fat should be chosen. It is currently believed that this recommendation is far more important in dogs than in cats.

In dogs or cats that do vomit relentlessly, the patient should be held NPO for 3 to 4 days. In cats alternative routes to oral alimentation must be pursued if the cat has been anorectic before presentation or if there is evidence to support concurrent hepatic lipidosis. After holding a patient NPO water is slowly reintroduced, followed by small amounts of a carbohydrate-rich and low-fat diet.

Analgesia

Abdominal pain is the key clinical sign in human patients with pancreatitis and is recognized in excess of

90% of all pancreatitis patients. Abdominal pain is much more commonly recognized in dogs than in cats with pancreatitis, but even in dogs the reported rate of abdominal pain is only approximately 58%. It is unlikely that abdominal pain occurs less frequently in dogs than in cats and it is much more likely that abdominal pain remains unidentified in veterinary species. Thus, the presence of abdominal pain should be assumed and analgesic drugs are indicated in all small animal patients with pancreatitis. Meperidine, butorphanol tartrate, morphine, fentanyl, or combinations of multiple analgesic drugs can be used in hospitalized patients. Outpatients can be treated with oral butorphanol, tramadol, or a fentanyl patch.

Antiemetic Agents

Until recently the choices for antiemetic agents for use in dogs and cats with pancreatitis was limited. Metoclopramide, a dopamine inhibitor, was most widely used. However, it's effect on splanchnic perfusion remains in question and the author does not like to use metoclopramide in dogs or cats with pancreatitis. Fortunately, several other antiemetic agents have become available over the last few years. Dolasetron is a $5HT_3$ antagonist and is a very effective antiemetic agent in both dogs and cats. The injectable formulation of dolasetron can be used for intravenous, subcutaneous, and oral administration and is being used at 0.3 to 0.6 mg/kg every12–24 hours in both dogs and cats. Recently, a new drug, maropitant, an NK_1 antagonist, has become available in both Europe and the US. Initial experiences in dogs are good, but there is little experience in cats and the drug is currently not licensed for use in cats.

Plasma

Studies in dogs suggest that when α_2-macroglobulin, one of the scavenger proteins for activated proteases in serum, is depleted death ensues rapidly. Fresh frozen plasma (FFP) and fresh whole blood not only contain α_2-macroglobulin, but also albumin, which has many beneficial effects in patients suffering from severe pancreatitis. In clinical trials in human patients with acute pancreatitis there was no benefit of plasma administration. However, FFP is widely believed to be useful in dogs with severe forms of pancreatitis.

Antibiotics

In contrast to human beings, infectious complications of pancreatitis are rare in dogs and cats with pancreatitis. Also, even though such complications occur frequently in human pancreatitis patients and are estimated to be responsible for approximately 25% to 50% of all deaths associated with acute pancreatitis, a clear advantage of antibiotic use has not been demonstrated to date. Therefore, the use of antibiotic agents should be limited to those cases when an infectious complication can be identified or is strongly suspected.

Anti-inflammatory Agents

There are no data on the use of anti-inflammatory agents in dogs and cats with severe pancreatitis, but no benefit was found in human patients with acute pancreatitis. In dogs and cats with severe pancreatitis corticosteroids should only be used in secondary cardiovascular shock. Corticosteroids may be needed to treat small animal patients with IBD and concurrent mild chronic pancreatitis, and do not appear to be harmful in these patients.

Other Therapeutic Strategies

Many other therapeutic strategies, such as the administration of trypsin-inhibitors (eg, trasylol), platelet activating factor inhibitors (PAFANTs), dopamine, antacids, antisecretory agents (ie, anticholinergics, calcitonin, glucagon, somatostatin), or selenium, and peritoneal lavage all have been evaluated in human patients with pancreatitis. With the exception of PAFANTs and selenium, none of these have shown any beneficial effect at this point. The efficacy of selenium, which has also been shown to decrease mortality in dogs with pancreatitis in an uncontrolled study, needs to be further evaluated before its use can be recommended. Also, dopamine has been shown to be useful in preventing progression of pancreatitis when administered within 12 hours of initiating pancreatitis. While this time limit would preclude dopamine to be effective in routine therapy of pancreatitis, patients with pancreatitis that have to undergo anesthesia may benefit from treatment with dopamine during the procedure.

Mild Chronic Pancreatitis

It should also be noted that many patients, both canine and feline, have mild forms of chronic pancreatitis. Oftentimes these patients have concurrent conditions, most notably inflammatory bowel disease (IBD). Very little is known about appropriate therapy for these animals and management is often limited to evaluation and treatment of the concurrent condition, and careful monitoring of the pancreatitis. Serum calcium and triglyceride concentrations should always be evaluated in the patients in order to identify any risk factors that can potentially be addressed therapeutically. Also, the use of low fat diets is recommended in these patients. This is especially important in dogs where an ultra-low-fat diet should be chosen. Over the last two decades a new form of pancreatitis, autoimmune-mediated pancreatitis has been described in humans. Autoimmune-mediated pancreatitis is now commonly recognized in humans and is characterized by a lymphocytic-plasmacytic infiltration of the pancreas. Human patients with immune-mediated pancreatitis respond favorably to the administration of corticosteroids. Recently, several clinicians have started to cautiously treat canine and feline patients with chronic pancreatitis with corticosteroids and have found this treatment strategy to be beneficial in a portion of cases. In a recent pilot study the use of superoxide dismutase was shown to have a beneficial affect in dogs with subclinical chronic pancreatitis. Further studies are needed to confirm such a beneficial effect in dogs with more severe disease.

Just like human patients with chronic pancreatitis, canine and feline patients with chronic pancreatitis are at risk for developing episodes of severe pancreatitis at any time or exocrine pancreatic insufficiency and diabetes mellitus later in life.

Prognosis

The prognosis for dogs and cats with pancreatitis is directly related to disease severity, extent of pancreatic necrosis, occurrence of systemic and pancreatic complications, duration of the condition, and the presence of concurrent disease.

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CHRONIC SMALL INTESTINAL DISEASE

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Small intestinal disease can be acute or chronic. Acute small intestinal disease is most commonly dietary due to ingestion of food that leads to an adverse reaction, infectious due to Parvovirus enteritis or other enteric pathogens, or mechanical due to foreign bodies, intussusceptions, or torsions. Chronic small intestinal disease can be infectious, inflammatory, mechanical, or neoplastic.

CHRONIC SMALL INTESTINAL DISORDERS

Dogs with chronic small intestinal disorders usually present for chronic diarrhea and may or may not display other clinical signs such as vomiting, weight loss, flatulence, or borborygmus. The most common cause for chronic small intestinal disease in dogs and cats is idiopathic inflammatory bowel disease (IBD). Dogs also commonly have small intestinal bacterial overgrowth (SIBO). Other common small intestinal disorders are intestinal neoplasia, infectious causes such as chronic infections with a pathogenic organism, fungal infections, enteric protozoal or helminthic parasites, or partial obstructions. A detailed discussion will be limited to IBD and SIBO.

IBD

IBD in human patients defines a syndrome of chronic diarrhea due to Crohn's disease or ulcerative colitis. Both Crohn's disease and ulcerative colitis are idiopathic disorders but are defined by specific criteria. In dogs and cats there is no universally accepted definition for IBD. The author defines IBD as any inflammatory condition of the intestine no matter what the predominant cell type or the underlying etiology. In some cases of IBD a cause may be identified. For example, intestinal parasites may cause eosinophilic inflammation and some bacterial infections may cause neutrophilic inflammation. However, in the majority of cases inflammatory bowel disease remains idiopathic. Some investigators include only cases of idiopathic inflammation of the intestine to define the term IBD, while others distinguish between idiopathic IBD and IBD due to a specific cause.

Chronic diarrhea is the most common clinical sign observed in dogs and cats with IBD. Weight loss is also commonly observed. Vomiting is observed when the stomach is involved, but can also occur in cases that are limited to the intestinal tract.

A diagnosis of IBD is usually based on histopathologic evaluation of intestinal biopsy specimens, most commonly collected during gastroduodenoscopy. Histopathology is accepted as a gold standard for diagnosing IBD. However, histopathology is not without limitations. Good quality samples must be submitted in order for the histopathologist to be able to interpret the sections. Also, there is a large degree of variability of the number of inflammatory cells seen in biopsy specimens of normal dogs and objective criteria for a diagnosis of IBD have not been universally agreed upon. Still, histopathology can be useful in the clinical evaluation of dogs and cats with suspected IBD. However, the histopathologic diagnosis needs to be carefully evaluated in light of all the other patient information available. If the histopathologic diagnosis of the biopsy does not fit the patient this should be discussed with the pathologist who interpreted the sections.

There are an increasing number of non-invasive tools to assess function and pathology of the gastrointestinal tract. Serum folate can be decreased in proximal and diffuse small intestinal disease. Serum cobalamin can be decreased in distal or diffuse small intestinal disease, exocrine pancreatic insufficiency, or small intestinal bacterial overgrowth. Fecal α_1-proteinase inhibitor concentration can be used to assess gastrointestinal protein loss. Serum C-reactive protein can be used as a marker for intestinal inflammation. Also, evaluation of serum and tissue levels of cytokines may be useful in the definition of specific subsets of IBD in dogs and cats.

Treatment of IBD is rather empiric and involves dietary trials, antibiotic agents, if a bacterial etiology is suspected, and antiinflammatory and immunosuppressive agents. Cobalamin supplementation is necessary in many patients with IBD that also have cobalamin deficiency as evidenced by a severely decreased serum cobalamin concentration. The most commonly used antiinflammatory and immunosuppressive agent in both dogs and cats is prednisone or prednisolone. Dogs should be treated with 2 mg/kg twice a day per os (PO) for 5 days, followed by 1 mg/kg twice a day for 6 weeks, 0.5 mg/kg twice a day for 6 weeks, 0.5 mg/kg once a day for 6 weeks, and 0.5 mg/kg every other day for 6 weeks. Cats can be treated slightly more aggressively with 2 mg/kg twice a day per os for 10 days, followed by a decreasing dosing schedule similar to the one used in dogs. If the patient has a relapse the steroid dose should be increased to the last highest dose used.

If the patient develops intolerable side effects from steroid use, budesonide can be used. Budesonide is a locally active steroid that has a very high first pass effect in the liver and has thus is associated with few systemic side effects. Big dogs can take the human 3 mg capsule orally once a day. In smaller dogs and cats capsules must be reformulated in order to avoid severe gastrointestinal side effects.

Other immunosuppressive agents that are being used for canine IBD are azathioprine, cyclophosphamide, and cyclosporine. However, very little is known about use of these drugs in canine or feline patients with IBD and their routine use can not be recommended at this time.

Recently, a clinical index has been described that can be used to classify the severity of IBD in clinical patients. Similar systems have been used successfully for objective assessment of disease severity in humans with IBD for many years.

SIBO

Small intestinal bacterial overgrowth (SIBO) is a qualitative and/or quantitative derangement of the small intestinal microflora that leads to clinical signs of small bowel diarrhea. Under normal conditions the small intestine only harbors a small number of bacteria of mostly aerobic species. Many authors believe that normal dogs have less than 10^4 to 10^5 bacteria per mL of duodenal juice. However, other authors have reported much higher bacterial counts in duodenal juice. Quantitative culture of duodenal juice can be technically demanding and it is possible that different clinical microbiology laboratories would have different results for the same sample. There also may be other factors that influence the results of duodenal cultures. For example, endoscopic technique may influence the consistency of the sample and speed of transport and plating may have an effect on the yield of colonies, especially those of obligate anaerobic species. Finally, these findings could be a reflection of differences in husbandry and nutritional management between pet dogs and research dogs. For example, research dogs are often exposed to fecal matter and coprophagia tends to be more common in these dogs. Having said all of this, there is no doubt that there is a large degree of variability of the normal small intestinal microflora between dogs.

Etiology

An abnormal proliferation of bacteria and the change in bacterial species causes SIBO. However, SIBO is not a primary disorder in most if not all patients with this disorder. There are several protective mechanisms that prevent SIBO. Gastric acid, intestinal motility, and antibacterial activity of pancreatic juice all limit the bacterial microflora in the small intestine. Gastric acid directly destroys bacteria that are ingested with the diet and also decreases the pH in the ingesta leading to a lower pH in the proximal small intestine. However, the lack of gastric acid secretion alone is not sufficient for SIBO to develop. Propulsive movements of the small intestine are probably the most important protective factor since there is no physical barrier between the large intestine and the small intestine that would prevent retrograde cultivation of the small intestine by the large intestinal microflora. The antibacterial properties of pancreatic juice are not well understood. Pancreatic digestive enzymes may be partly responsible for the antibacterial action of pancreatic juice.

Any disease process that affects one or more of the protective mechanisms discussed can ultimately lead to SIBO. For example, SIBO is commonly observed in dogs with exocrine pancreatic insufficiency. However, in many dogs with small intestinal bacterial overgrowth a primary disease process cannot be identified.

Pathophysiology

Bacteria in the small intestinal lumen are metabolically active. This affects the host in many ways. Bacteria compete with the host for nutrients. One example is the water-soluble vitamin cobalamin. Under physiologic conditions cobalamin is absorbed in the ileum. Especially anaerobic bacteria effectively compete for dietary cobalamin leading to a decreased cobalamin absorption and, over time, to a depletion of cobalamin body stores and hypocobalaminemia. Bacteria also produce a variety of substances. For example, bacteria synthesize folic acid and vitamin K, which can lead to an increased serum folate concentration. This does not appear to have any pathologic effect on the host. Some bacterial species also produce bacterial proteases and glycosidases, short chain fatty acids, unconjugated bile acids, ethanol, enterotoxins, endotoxins, and peptidoglycan polysaccharide polymers. These substances can be toxic to the enterocytes or damage the brush border. Additionally, these substances can be absorbed from the small intestine and can lead to hepatic toxicity or even systemic effects, though clinically significant hepatotoxicity and systemic effects are rare in dogs with SIBO.

The increased production of short chain fatty acids leads to a decreased intraluminal pH in the small intestine and to an increased osmotic load. Medium and long chain fatty acids have a more direct effect on fluid absorption and can even stimulate fluid secretion, contributing to the pathogenesis of diarrhea in dogs with SIBO. Also, fatty acids can undergo hydroxylation and hydroxylated fatty acids further inhibit fluid absorption and increase fluid secretion. Bacteria in the small intestinal lumen also deconjugate bile acids. Bile acids play an important role in fat digestion by emulsifying dietary fats. During SIBO bile acids are deconjugated and reabsorbed and are no longer available for fat emulsification. This can lead to fat malabsorption and in extreme cases to steatorrhea. Fat malabsorption further increases the fatty acid load in the intestinal lumen leading to further inhibition of fluid absorption and diarrhea. Fat malabsorption also can be associated with malabsorption of fat-soluble vitamins. Finally, SIBO can lead to the destruction of the brush border, leading to protein- and carbohydrate malabsorption.

While there are many functional changes that are caused by SIBO, in most cases there are no morphologic changes that can be visualized by light microscopy. In insolated cases villous blunting and mild lymphocytic-plasmacytic inflammation maybe observed, but SIBO may be secondary to intestinal inflammation rather than be the cause of it.

Clinical Findings

SIBO in dogs leads to chronic small bowel diarrhea that is often intermittent. Weight loss can be present in some cases. Other clinical signs maybe due to the primary underlying disease process such as partial obstruction, exocrine pancreatic insufficiency, or others. Complete blood count and serum chemistry profile are within normal limits in most cases, but mild elevations in hepatic enzyme activities can be observed. Abdominal radiographs and ultrasound may reveal findings that implicate an underlying disease process but otherwise will not reveal any specific findings.

Diagnosis

Part of the controversy about SIBO is due to the fact that this disorder is difficult to diagnose. The most conclusive diagnostic modality is the culture of duodenal juice. However, not only is the collection of duodenal juice challenging, but also the culture of duodenal juice once collected is difficult, time-consuming, and expensive and requires a laboratory that has experience in this area. Therefore, culture of duodenal juice is usually limited to academic institutions.

Several noninvasive diagnostic tests that have been found to be useful in human patients suspected of having SIBO and have also been evaluated in dogs with suspected SIBO:

Serum folate concentration – As pointed out previously folic acid is synthesized by enteric bacteria and is available for absorption. If SIBO is present for a long period of time serum folate concentrations increase. While an increased serum folate concentration is fairly specific for SIBO it is not very sensitive. In one study only 50% of all dogs with SIBO had increased serum folate concentrations.

Serum cobalamin concentration – Many species of bacteria utilize cobalamin and compete with the body for dietary supplies. Unlike an increased serum folate concentration a decreased serum cobalamin concentration is not specific for SIBO. Any severe small intestinal disease involving the ileum can lead to cobalamin deficiency. Also, a lack of intrinsic factor and digestive proteases in dogs with exocrine pancreatic insufficiency can cause cobalamin deficiency. A decreased serum cobalamin concentration is rather insensitive for SIBO and in one study only 25% of dogs with SIBO had decreased serum cobalamin concentration. A combination of a decreased serum cobalamin and an increased serum folate concentration is highly specific for SIBO but rather insensitive. These two parameters are to date the most practical diagnostic tools for the diagnosis of SIBO in a private practice setting.

Other noninvasive diagnostic tests, previously evaluated for the diagnosis of SIBO, such as unconjugated bile acid concentration in serum, breath hydrogen concentration, and C-xylose and C-bile acid tests have not shown to be useful for the diagnosis of this condition.

Treatment

The therapeutic goal in dogs with SIBO is the identification and treatment of the inciting cause. For example, serum TLI concentration should be evaluated. Dogs with EPI and secondary SIBO usually do not require specific therapy for SIBO once they are treated with enzyme supplementation.

If a primary cause can not be identified the dog should be treated with antimicrobial therapy. Oxytetracycline (10–20 mg/kg q 8–12 hr PO for 4–6 weeks) used to be the therapy of choice. Unfortunately, oxytetracycline has become largely unavailable. Tylosin (25 mg/kg BID for 6 weeks) is the new antibiotic agent of choice. Other antibiotics, such as metronidazole can also be used. Some dogs respond to therapy rapidly and do not have a recurrence. However, other dogs do not respond to antibiotic therapy alone. If there is no marked improvement after 2 weeks of appropriate antibiotic therapy further work up is necessary. Some dogs may respond to therapy with a complete resolution of clinical signs but may have a recurrence of clinical signs as soon as antibiotic therapy is discontinued. These patients require a further diagnostic work up. In some of these patients a specific underlying cause of the SIBO can be identified and treated accordingly. However, in some dogs no specific cause can be identified and prolonged, maybe even life-long, antimicrobial therapy is required. Also, in a recent study the use of fructooligosaccharides (FOS) in the diet showed a lasting advantageous effect. Thus, the author recommends the use of a FOS-containing diet in combination with antibiotic therapy.

If serum cobalamin concentration is decreased below the lower limit of the reference range cobalamin should be supplemented parenterally.

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NEW DEVELOPMENTS IN THE DIAGNOSIS OF FELINE PANCREATITIS

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The incidence of exocrine pancreatic disorders is quite large in cats. In a large retrospective study of necropsy findings, 1.3% of 6,504 feline pancreata showed significant pathological lesions. In a more recent study, 115 cats were evaluated at necropsy. At least 3 biopsies were collected from each pancreas and each biopsy was assessed separately for evidence of pancreatitis. The results were very surprising in that only 33% of cats had no evidence of pancreatitis, 15.7% had evidence of acute pancreatitis, and 60% had evidence of chronic pancreatitis. These necropsy findings are contrasted by clinical data from 180,648 cats entered into the Veterinary Medical Data Base (VMDB) at Purdue University over a 10-year period, of which only 0.57% (1,027) were diagnosed with exocrine pancreatic disorders.[3] Thus it appears that, while cats are affected with diseases of the exocrine pancreas nearly as frequently as dogs, these disorders often escape definitive diagnosis.

CLINICAL PICTURE

Clinical signs in cats with pancreatitis, even when severe, present with nonspecific clinical signs. In one study of 40 cats with severe pancreatitis the following clinical signs were reported: lethargy (100%), anorexia (97%), dehydration (92%), hypothermia (68%), vomiting (35%), abdominal pain (25%), a palpable abdominal mass (23%), dyspnea (20%), ataxia (15%), and diarrhea (15%). Especially remarkable is the low incidence of vomiting and abdominal pain, both of which are common clinical signs in human and canine pancreatitis patients. Clinical signs in patients with pancreatitis are due to pancreatic inflammation or systemic complications of the pancreatic inflammation. While clinical signs are not specific for pancreatitis, vomiting and cranial abdominal pain are key clinical signs in humans and dogs with pancreatitis, but cats display these key clinical signs much less frequently.

DIAGNOSTIC TESTS

Complete blood count and serum chemistry profile often show mild and nonspecific changes. More severe changes can be observed in patients with severe forms of pancreatitis. Serum amylase and lipase activities are of no clinical value for the diagnosis of feline pancreatitis. Radiographic changes seen in some cases include a decreased contrast in the cranial abdomen and displacement of abdominal organs. However, these changes are rather subjective and abdominal radiography is nonspecific for feline pancreatitis. Abdominal ultrasound is useful in the diagnosis of pancreatitis in cats. The sensitivity of abdominal ultrasonography is up to 35% in cats. However, these numbers are largely operator-dependent. Changes identified include pancreatic swelling, changes in echogenicity of the pancreas (hypoechogenicity in cases of pancreatic necrosis and, less commonly, hyperechogenicity in cases of pancreatic fibrosis) and of peripancreatic fat (hyperechogenicity in cases of peripancreatic fat necrosis), fluid accumulation around the pancreas, and less frequently a mass effect in the area of the pancreas. Abdominal computed tomography is a routine procedure in humans suspected of having pancreatitis, but appears to be very insensitive for the diagnosis of pancreatitis in the cat.

Trypsin-like immunoreactivity (TLI) is specific for exocrine pancreatic function. However, the sensitivity of serum TLI concentration for pancreatitis in cats is only approximately 30% to 60% making it a suboptimal diagnostic test for pancreatitis. However, serum TLI concentration remains the diagnostic test of choice for the diagnosis of EPI.

Recently, an assay for the measurement of pancreatic lipase immunoreactivity in cats (fPLI) has been developed and validated. Many different cell types in the body synthesize and secrete lipases. In contrast to catalytic assays for the measurement of lipase activity, use of immunoassays does allow for the specific measurement of lipase originated from the exocrine pancreas.

In a group of cats with experimentally induced pancreatitis both serum fTLI and fPLI concentrations did increase initially, but serum fPLI stayed elevated much longer than did serum fTLI concentration suggesting that serum PLI concentration is much more sensitive for pancreatitis than serum TLI concentration. In another study of cats with spontaneous pancreatitis, serum fPLI concentration was more sensitive and more specific than serum fTLI concentration or abdominal ultrasonography.

Thus, serum fPLI concentration is the most sensitive and specific diagnostic test for pancreatitis currently available for cats. Currently, this assay is only available through the Gastrointestinal Laboratory at Texas A&M University (www.cvm.tamu.edu/gilab).

Traditionally, a pancreatic biopsy was viewed as the most definitive diagnostic tool for pancreatitis. Pancreatic biopsies can be collected during abdominal exploratory or by laparoscopy. The presence of pancreatitis can be easily diagnosed by the gross appearance of the pancreas in many cases. However, the absence of pancreatitis can be difficult to prove as pancreatic inflammation is often highly localized. Thus, even if multiple biopsies are being collected, pancreatic inflammation, especially in cases of chronic pancreatitis, may easily be missed. It should also be noted that while a pancreatic biopsy in itself is not associated with many complications many patients with pancreatitis are poor anesthetic risks.

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HOW I TREAT INFLAMMATORY BOWEL DISEASE (IBD) IN DOGS

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It is important that the clinician formulate a treatment protocol based on a correlation of clinical course, laboratory and gross findings, and histologic findings rather than relying on histologic changes alone. Therapeutic intervention may include dietary therapy alone on a trial basis, or dietary therapy prescribed in combination with pharmacotherapy using either single agent or combination drug therapy. Drugs used in management of canine inflammatory bowel disease (IBD) may include corticosteroids (prednisone, dexamethasone, budesonide), metronidazole, azathioprine, and cyclosporine. Ancillary therapy can include other agents in selected cases, including probiotics, cobalamin, and various alternative therapies, and also acupuncture. It is emphasized that any concurrent disease, including parasitism (including *Giardia* and *Cryptosporidium*), bacterial overgrowth, and gastrointestinal (GI) hypomotility must be diagnosed and managed concurrently for best overall patient response.

Corticosteroids are the initial treatment of choice for lymphocytic-plasmacytic and eosinophilic enteritis in most cases. Mild to moderate cases (as determined by clinical signs, normal protein levels, and degree of inflammatory cell infiltrate on biopsy) often respond to prednisone at a dose of 0.5 to 1.5 mg/kg divided twice daily for 2 to 4 weeks followed by a gradual decrease in 50% increments at 2-week intervals. Alternate-day or every third day treatment can often be reached by 2 to 3 months. Occasionally treatment can be discontinued altogether by 3 to 6 months.

Moderate to severe cases and any case in which the total protein is less than 5.5 g/dL should be treated more aggressively using an initial prednisone dose of 2.2 mg/kg per day for 2 to 4 weeks before an attempt is made to decrease the dose. Use of combination drug therapy (prednisone and metronidazole) in these cases at the outset is recommended in order to improve chances of controlling clinical signs more quickly and to prevent progression of the disease.

If there is poor tolerance to prednisone, the next best options are to try either budesonide, metronidazole, or cyclosporine. **Budesonide** is one of a group of novel "locally acting" corticosteroids. Budesonide undergoes high first pass metabolism in the liver and 90% is converted into metabolites with low corticosteroid activity. It has minimal systemic availability. In general, budesonide is administered to small dogs at 1 mg administered once per day. It has been used at higher doses of 2 to 3 mg per day for larger dogs. Large dogs receive 3 mg once daily initially, and the dose is later tapered to alternate day administration for longer term use. The daily dose should not exceed 3 mg. Potential adverse effects include polyuria/polydipsia (PU/PD), when budesonide is used at the high end of the dose range, and GI ulceration.

Metronidazole has both an antibacterial and anti-inflammatory effect. Metronidazole is administered at 10 to 20 mg/kg two times daily. A major advantage of using combination therapy is that the corticosteroid dose can usually be decreased from the high initial dose in a timely manner, thus decreasing the likelihood of significant corticosteroid-related side effects. Also, I have successfully managed on a long-term basis canine patients with mild to moderate lymphocytic-plasmacytic enteritis that were intolerant to corticosteroids, with metronidazole alone.

Dogs with protein-losing enteropathy (PLE) with marked hypoproteinemia (total protein less than 4.5 g/dL) caused by lymphocytic-plasmacytic enteritis often respond well when an aggressive therapeutic course is undertaken (prednisone, metronidazole, azathioprine used in combination). **Azathioprine** is started early in PLE cases with IBD. The canine dose is 2–2.5 mg/kg once daily. If azathioprine is used at the outset, the prednisone dose is decreased by 50% from 2.2 mg/kg per day after 3 to 4 weeks or based on clinical improvement.

Azathioprine is generally used for 3 to 9 months in dogs. Once adequate control is achieved, the daily dose is decreased by 50%, and subsequently alternate-day therapy is used. Side effects are uncommon in dogs but may include anorexia, jaundice (hepatic damage), poor hair growth, and bone marrow suppression. In addition, it is suspected that azathioprine has the potential to induce pancreatitis. A complete blood count should be run to monitor for evidence of anemia or leukopenia at 3-week intervals for the first 2 months and then once every several months.

Cyclosporine A (cyA) has been shown to be effective in steroid-resistant IBD in humans and also perianal fistula management in both humans and dogs. A study was undertaken to evaluate the pharmacokinetics and clinical efficacy of oral cyA treatment in 14 dogs with steroid-refractory IBD (Allenspach K, et al, J Vet Intern Med 2006). Improvement was noted in 12 of 14 dogs. T-cell lysis is a possible mechanism of action. The anti-inflammatory effect of cyA in human IBD is believed to be due to suppression of activated T cells infiltrating the mucosa, thereby decreasing the amount of proinflammatory cytokines, and ultimately, the clinical signs of disease. The cyA dose used in the study of 14 dogs was 5 mg/kg SID. The sole therapy was cyA. Previous therapy had included immunosuppressive doses of steroids in all dogs and metronidazole was used in some.

Dietary therapy involves feeding either a limited ingredient/novel protein source diet or a hydrolyzed protein diet. In most cases, diets that are highly digestible and low-residue work best for small intestinal disease. If a decision is made to initially manage an animal with dietary therapy alone the dietary trial should be conducted for a minimum of 3 to 4 weeks. If biopsies reveal moderate to severe IBD and/or if there is any degree of patient compromise pharmacotherapy should be included in the treatment regimen along with dietary management. In my experience, animals with this degree of disease rarely respond to dietary manipulation alone. Studies are underway to further evaluate the effect of dietary therapy on management of IBD.

MANAGING THE VOMITING DOG

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Vomiting is a common clinical sign in small animals. Although vomiting is a protective mechanism developed to remove ingested noxious substances it also is associated with many disease conditions including those of the gastrointestinal system, other abdominal conditions, systemic or metabolic disease and drug toxicity, to name a few (Table 1). Severe vomiting can result also in serious consequences including volume depletion, acid-base and electrolyte disturbance, esophagitis, aspiration pneumonia, and malnutrition. An overview of the pathophysiology, potential etiologies, antiemetic therapy and a logical clinical approach to the chronic vomiting patient are presented in this article.

The act of vomiting is divided into three components; nausea, retching, and vomiting. Nausea precedes retching and is associated with salivation and swallowing. This is followed by motility changes in the GI tract with relaxation of the stomach and lower esophageal sphincter. Retching results from the forceful contractions of the abdominal muscles and diaphragm. Vomiting then occurs as gastric contents are forcefully expelled out of the mouth. The driving force is contraction of the abdominal muscles and diaphragm causing intrathoracic pressure changes from negative during retching to positive during vomiting.

Although vomiting is a complex and poorly understood event it is simply best described as a reflex act that is initiated by stimulation of the conceptualized "vomiting or emetic center" located in the medulla oblongata of the brain. Activation of the vomiting center occurs either through a humoral pathway initiated via blood-borne substances or by activation through various neural pathways leading to the vomiting center. It is also sometimes also classified as either centrally mediated (from CNS mediation) or peripherally mediated (from distant structures in the abdominal cavity). Understanding this concept helps one formulate a differential list of etiologies.

Neural stimulation of the vomiting center arises through either afferent vagal, sympathetic, vestibular, and cerebrocortical pathways. Activation of peripheral receptors found throughout the body can stimulate these neural pathways. Particularly important are receptors that are located throughout the abdominal viscera but especially those located in the duodenum, which contains the highest concentration and hence has been referred to as the "organ of nausea." Disease or irritation of the gastrointestinal tract, other abdominal organs, or peritoneum can directly stimulate vomiting through vagal afferent pathways. Receptors in the kidneys, uterus, and urinary bladder send afferent impulses via sympathetic nerves while receptors located in the pharynx and tonsilar fossae transmit impulses thorough afferent fibers of the glossopharyngeal nerve. Central nervous system (CNS) disease may directly stimulate the vomiting center such as direct extension of inflammatory stimuli, hydrocephalus or space occupying lesions. Cyclic vomiting in the dog has been associated with autonomic or visceral epilepsy arising from the limbic region.

The vomiting center is stimulated indirectly via a humoral or blood-borne factors by activating the chemoreceptor trigger zone (CRTZ) located in the area postrema. The blood–brain barrier is limited in this area that allows the CRTZ to be exposed to chemical stimuli found in the circulation. Blood-borne substances stimulating the CRTZ include certain drugs, uremic toxins, electrolyte, osmolar and acid–base disorders as well as a number of metabolic derangements. Drugs such as apomorphine or cardiac glycosides and bacterial toxins are examples. There is also evidence in the dog that vestibular stimulation passes through the CRTZ before activating the vomiting center. Motion sickness, inflammation of the labyrinth, or lesions in the cerebellum result in vomiting via this pathway.

ANTIEMETICS: THEIR SELECTION AND USE

Antiemetics are drugs used to control nausea and vomiting. When selecting an antiemetic for a vomiting patient it is important to have an idea as to the probable etiology so an appropriate class of antiemetic can be selected for the specific causes in each individual case. Antimetics should be used because they aid in controlling the nausea and vomiting, make the patient more comfortable, and may actually return them back to earlier state of positive nutrition. Antiemetics are also indicated when there is serious fluid and electrolyte loss with dehydration or from the fear of aspiration pneumonia. Antimetics should not be used if the patient has a GI obstruction in which surgery would be indicated or if the side effects of the antiemetic would contraindicate their use. There are some that believe antiemetics should not be used in the management of vomiting because they may mask the signs, therefore providing a false sense of security of clinical improvement and may consequently making the correct diagnosis. I believe this paradigm is shifting and now it is felt that antiemetics actually make the patient more comfortable. Antiemetic therapy, however, should not be an excuse for an accurate diagnostic workup.

Common antiemetic agents used in small animal verterinary medicine, the receptors they block, and their anatomic location and potential side effects are listed in Table 1.

A newer antiemetic recently approved for used in dogs is maropitant (Cerenia™). This is an NK1 antagonist that works in blocking vestibular, CRTZ, emetic center and peripherial input. I used this broad-spectrum antiemetic in a preliminary pre-launch trial of 50 vomiting cases. The drug was effective in controlling vomiting in most every case with virtually no side effects. This drug can be given subcutaneously (SQ) or orally once daily.

Table 1. Common Causes of Vomiting

Metabolic/Endocrine Disorders
- Uremia
- Hypoadrenocorticism
- Diabetes mellitus
- Hyperthyroidism
- Hepatic disease
- Endotoxemia/septicemia
- Hepatic encephalopathy
- Electrolyte disorders
- Acid-base disorders

Intoxicants
- Lead
- Ethylene glycol
- Zinc
- Strichnine

Drugs
- Cardiac glycosides
- Erythromycin
- Chemotherapy agents
- Apomorphine
- Xylazine
- Penicillamine
- Tetracycline
- NSAIDs

Dietary
- Indiscretions
- Intolerances
- Allergy

Gastric Disorders
- Gastritis
- Helicobacter
- Parasites
- Ulceration
- Neoplasia
- Foreign bodies
- Dilatation-volvulus
- Hiatal hernia
- Obstruction
- Motility disorders

Small Intestinal Disorders
- Inflammatory bowel disease
- Neoplasia
- Foreign body
- Intussusception
- Parasites
- Parvovirus
- Bacterial overgrowth

Large Intestinal Disorders
- Colitis
- Obstipation
- Parasites

Abdominal Disorders
- Pancreatitis
- Peritonitis
- Neoplasia
- Hepatobilary disease

Table 2. Antiemetic Agents Used in Small Animal Veterinary Medicine

Drug	Mode of Action	Location of Action
Antihistamines	Block cholinergic and histaminergic receptors	Vestibular, CRTZ
Phenothiazines	Alpha-2 antagonists	Emetic center, CRTZ
Propantheline, isopropamide	Anticholinergic	CRTZ, peripherial
Metoclopramide	Antidopaminergic	CRTZ
Ondansetron, dolasetron	Serotonin (5HT3) antagonists	Emetic center, CRTZ, peripherial
Maropitant (Cerenia™)	Neurokinin-1 (NK-1) antagonists	Emetic center, CRTZ, peripherial

CLINICAL APPROACH

When dealing with the vomiting patient there are four important things to determine in the history: 1) is the patient actually vomiting, 2) a detailed vomiting history, 3) drug and diet history, and 4) other signs or symptoms associated with the vomiting. The history should confirm the patient is truly vomiting and that the signs described are not associated with gagging, coughing, dysphagia or regurgitation which the client may confuse with vomiting. In some cases, this may be difficult to differentiate based on the history alone.

The signalment may also be helpful for example, young unvaccinated patients are more susceptible to infectious disease such as parvovirus or distemper while an older animals generally would bring about a different set of differentials. Vaccination status, travel history, previous medical problems, as well as medication history should be determined. In particular it should be noted if nonsteroidal anti-inflammatory drugs (NSAIDs) have been used. Questions should also investigate concurrent signs that may occur with systemic or metabolic disease. For example, polydipsia, polyuria, and weight loss are typical for vomiting associated with diabetic ketoacidosis or chronic renal failure.

The history should then focus on the actual vomiting episodes. As in the old television series Dragnet when Friday says " D'facts madam give me only D'facts," D'FACTs one should obtain are: D) duration, F) frequency, A) association with eating or drinking, C) character of the vomitus and T) treatments that have been given for the vomiting. A dietary history including the type of diet or recent diet change is equally important because vomiting may be associated with an adverse reaction to food. Vomiting in the immediate postprandial period may suggest an adverse reaction to food or possibly simply overeating. Vomiting undigested or a partially digested meal, especially when it is greater than 6 to 8 hours following eating, a point at which the stomach should normally be empty, suggests a gastric outflow obstruction or a primary gastric hypomotility disorder. Gastric outflow obstructions occur from foreign bodies, mucosal hypertrophy, tumors or polyps. Vomiting of a bile-tinged fluid, especially in the early morning hours often results from enterogastric reflux syndrome. The presence of blood in the vomitus either as fresh "bright red" blood or digested blood that has a "coffee grounds" appearance indicates gastrointestinal erosion or ulceration. Hematemesis with metabolic-related ulcers such as hypoadrenocorticism or uremia, drug-induced ulceration, gastritis, or gastric neoplasia are possible etiologies.

A complete physical examination may provide important information. Careful evaluation for other abnormalities can be a clue to the etiology of vomiting. The abdomen should be carefully palpated for bowel distention, effusion, masses or organomegaly. A rectal examination provides characteristics of colonic mucosa and feces. Melena suggests upper gastrointestinal bleeding and the presence of foreign material in the feces helps support a foreign body etiology. Patients having colitis or the severely obstipated animal will also often vomit.

DIAGNOSTIC PLAN

The history, physical examination, and basic laboratory findings should direct the clinician to a diagnosis or the next step in the workup. Most cases of acute vomiting are associated with a "garbage gut"; in these cases, little to no diagnostics are required and a response to symptomatic therapy confirms the diagnosis. In severe cases or those that have chronic vomiting, laboratory diagnostics are indicated and should include a minimum data base (complete blood count [CBC], biochemical profile and urinalysis) fecal examination and abdominal radiographs. This basic evaluation is essential in excluding all non-gastrointestinal causes of vomiting. If no abnormalities are identified the chronic vomiting patient should next be classified as either having mild disease with minimal debilitation or those having a significant history with serious debilitation. Those patients having significant or serious disease will require an in-depth diagnostic workup with emphasis on the gastrointestinal tract including contrast studies, ultrasound examination, and endoscopy. Animals that fail to respond to symptomatic therapy will also require in-depth diagnostic workup.

Animals with mild signs and minimal debilitation should first have dietary manipulation with food trials and treatment for gastrointestinal parasites. These therapeutic trials are very appropriate in this classification of cases. Adverse reactions to food consists of either food allergies or food intolerances. Intolerances refer to direct reactions to a specific substance in the diet such as a preservative or dye while an allergy is a specific immunologic reaction mediated against a protein antigen. Both can result in variable inflammatory gastric mucosal changes and vomiting. Dietary food intolerances are probably the most common cause of chronic intermittent vomiting. Most animals appear healthy and have only intermittent vomiting, primarily food, shortly following eating. Removal of the agent often results in prompt improvement. Food allergies are the result of a reaction to a specific protein antigen, usually the major antigen in the diet.

Animals suspected of having food related reactions should be placed on a hypoallergenic diet for at least a 2-week trial. Although food allergies causing dermatologic signs may take prolonged diet trials for a response to occur GI-related signs tend to respond within several weeks. There is no universal ideal diet and various dietary trials may be required. If the patient is dietary responsive that supports the diagnosis.

Parasites must always be considered when dealing with chronic vomiting in animals with little debilitation. Giardia, ascarids, and whipworms are usually diagnosed using proper fecal examination techniques. Physaloptera infection in dogs is uncommon but may be underestimated due to difficulty of diagnosis. Prevalence rates in the United States range from 1% to 25%. The worm burden need not be large to cause clinical signs. It is not unusual to find only one or two worms causing significant clinical signs include chronic intermittent vomiting. The adults produce few eggs and because the eggs are larvated, they may not float during routine fecal flotation. The diagnosis is most frequently made during endoscopy by simply viewing the parasite in the stomach or proximal duodenum. When symptomatic therapy is indicated with the chronic vomiting case anthelmintic trial therapy will rule out parasites as a cause. I usually prescribe febendazole at 50 mg/kg daily for 3 to 5 days.

An in depth GI evaluation should be considered in the vomiting animal with significant or severe gastric or gastrointestinal disease or in the patient that has failed to respond to adequate dietary and anthelmintic therapy. Persistent vomiting, hematemesis, weight loss and debilitation signify further diagnostic evaluation. Diagnostic techniques of the stomach involve radiology, ultrasonography, endoscopy and/or surgery. Radiology should be performed when a gastric lesion, foreign body, or outflow obstruction is suspected. My preferred means of evaluating the stomach using contrast radiology is performing a double contrast gastrogram. The technique involves administering barium sulfate suspension (1–2 mL/kg) via stomach tube, then rolling the patient to coat the mucosa and replacing the stomach tube and distending the gastric lumen with air. If sedation is required acepromazine should be used as it causes limited alteration in gastric motility. This technique gives good mucosal delineation and identifies intraluminal foreign bodies or lesions. If no lesion is identified additional barium can be then given to perform a standard upper gastrointestinal study.

Barium mixed with food appears to be a better test of gastric emptying for disorders of motility. As a general rule barium mixed with a standard meal should empty by 8 to 10 hours. Animals with markedly prolonged emptying time following a barium meal are considered to have a gastric motility disorder.

Endoscopy offers the best means of examining the gastric mucosal surface and lumen and to obtain a gastric mucosal biopsy. When evaluating the vomiting patient I always obtain duodenal biopsies to rule out inflammatory bowel disease, gastric mucosal brush cytology for *Helicobacter,* and obtain a gastric mucosal biopsy sample for urea culture for *Helicobacter.*

If endoscopy is not available then a surgical exploratory and full thickness biopsy may be indicated. One should evaluate the entire abdomen taking careful note of the liver, pancreas, and bowel. Full thickness biopsy of the duodenum, jejunum, and ileum in addition to the stomach is always performed in patients with gastrointestinal signs.

GASTRIC DISORDERS

If non-gastric causes of vomiting have been eliminated then gastric etiologies should then be considered. Gastric disorders can be simply grouped into conditions of mucosal involvement, those causing gastric out-flow obstruction, and gastric motility disorders. Inflammatory gastric mucosal disorders most commonly include lymphocytic-plasmacytic, eosinophilic or granulomatous gastritis. These conditions are diagnosed by biopsy. Inflammatory gastric disease may occur alone or in conjunction with inflammatory changes in bowel. The role of *Helicobacter* sp in gastric disease is uncertain because the organism is found in many normal dogs and cats. However, dogs having *Helicobacter* and concurrent gastritis should be treated as such and many will improve. Current recommendations of helicobacter include combinations of metronidazole and amoxicillin in combination with an acid blocking drug for 2 to 3 weeks. Other antibiotic combinations have also been used as well. Less common mucosal disorders include conditions causing gastric ulcerations, fungal disease, and neoplasia.

Conditions causing gastric outflow obstructions most often are associated with gastrointestinal foreign bodies or neoplasia. Antral-pyloric mucosal hypertrophy is a uncommon condition characterized by hypertrophy of the mucosa in the antral and pyloric region of the stomach that causes obstruction of gastric outflow. It is associated with chronic vomiting of food or gastric secretions. The diagnosis is made by identifying gastric retention on a barium contrast study with distinct mucosal folds in the antral region of the stomach. The therapy involves surgery and generally has a good prognosis.

If inflammatory and obstructive gastric disorders have been eliminated then gastric motility disorders should be considered. Most gastric motility disorders result in delayed gastric emptying with gastric retention and vomiting. The vomiting may occur at any interval following a meal. The relationship to eating is important however as the normal stomach should be empty of a meal in approximately 8 to 10 hours. Vomiting of a meal greater than 10 hours following eating is suggestive of a gastric retention disorder. Animals often respond to frequent semi-liquid diets and gastric prokinetic agents such as metoclopramide, cisapride or erythromycin.

A common condition observed in dogs the bilious vomiting syndrome or reflux gastritis. It is generally associated with early morning vomiting of bile without food. It is thought to result from reflux of duodenal fluid into the gastric lumen thus causing gastric mucosal irritation. Reflux may in part be associated with abnormal gastric motility however, duodenal disorders should be ruled out first. Most dogs respond to either a late bedtime meal and/or prokinetic agents.

CATS WITH COLITIS: PATHOGENESIS, DIAGNOSIS AND THERAPY

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CLINICAL CRITERIA

The colitis form of inflammatory bowel disease (IBD) has been defined clinically as a spectrum of gastrointestinal disorders associated with chronic inflammation of the colon of unknown etiology. A clinical diagnosis of IBD is considered only if affected cats have:

(1) Persistent (>3 weeks in duration) gastrointestinal signs (anorexia, vomiting, weight loss, diarrhea, hematochezia, mucousy feces)
(2) Failure to respond to symptomatic therapies (parasiticides, antibiotics, gastrointestinal protectants) alone
(3) Failure to document other causes of colitis by thorough diagnostic evaluation
(4) Histologic diagnosis of benign colonic inflammation

Large bowel forms of IBD have been reported in both dogs and cats, although large bowel IBD appears to be more prevalent in the dog.

PATHOGENIC CRITERIA

Known causes of colonic diarrhea should first be considered: food sensitivity reaction, bacterial infection, parasitic infection, fungal infection, and colonic neoplasia. Most current hypotheses on the pathogenesis of IBD hold that the gut has sustained reactivity to endogenous bacterial and/or food antigens.

HISTOLOGIC CRITERIA

IBD has been defined histologically by the type of inflammatory infiltrate (neutrophilic, eosinophilic, lymphocytic, plasmacytic, granulomatous), associated mucosal pathology (villus atrophy, fusion, crypt collapse), distribution of the lesion (focal or generalized, superficial or deep), severity (mild, moderate, severe), mucosal thickness (mild, moderate, severe), and topography (cecum, ascending colon, descending colon). Subjective interpretation of large intestinal IBD lesions has made it difficult to compare tissue findings between pathologists. Subjectivity in histologic assessments has led to the development of several IBD grading systems.

IMMUNOLOGIC CRITERIA

IBD has been defined immunologically by the innate and adaptive response of the mucosa to gastrointestinal antigens. Although the precise immunologic events of canine and feline IBD remain to be determined, a prevailing hypothesis for the development of IBD is the loss of immunologic tolerance to the normal bacterial flora or food antigens, leading to abnormal T-cell immune reactivity in the gut microenvironment. Genetically engineered animal models (eg, IL-2, IL-10, and T-cell receptor knockouts) that develop IBD involve alterations in T-cell development and/or function suggesting that T-cell populations are responsible for the homeostatic regulation of mucosal immune responses. Immunohistochemical studies of canine and feline IBD have demonstrated an increase in the T-cell population of the lamina propria, including CD3+ cells and CD4+ cells, as well as macrophages, neutrophils, and IgA-containing plasma cells. Many of the immunologic features of canine and feline IBD can be explained as an indirect consequence of mucosal T-cell activation. Enterocytes are also likely involved in the immunopathogenesis of IBD. Enterocytes are capable of behaving as antigen-presenting cells, and interleukins (eg, IL-7 and IL-15) produced by enterocytes during acute inflammation activate mucosal lymphocytes. Up-regulation of Toll-like receptor 4 (TLR4) and Toll-like receptor 2 (TLR2) expression contribute to the innate immune response of the colon. Thus, the pathogenesis and pathophysiology of IBD appears to involve the activation of a subset of $CD4^+$ T cells within the intestinal epithelium that overproduce inflammatory cytokines with concomitant loss of a subset of $CD4^+$ T cells, and their associated cytokines, which normally regulate the inflammatory response and protect the gut from injury.

PATHOPHYSIOLOGIC CRITERIA

Immune Responses

A generic inflammatory response involving cellular elements (B and T lymphocytes, plasma cells, macrophages, and dendritic cells), secretomotor neurons (eg, VIP, substance P, and cholinergic neurons), cytokines and interleukins, and inflammatory mediators (eg, leukotrienes, prostanoids, reactive oxygen metabolites, nitric oxide, 5-HT, IFN-γ, TNF-α, and platelet-activating factor) is typical of canine and feline inflammatory bowel disease. There are many similarities between the inflammatory response of the small and large intestine, but recent immunologic studies suggest that IBD of the canine and feline colon may be more of a Th1 type response with elaboration of IL-2, IL-12, INF-γ, and TNF-α.

Motility Changes

Experimental studies of the colitis form of IBD have shown that many of the clinical signs are related to motor abnormalities of the gastrointestinal tract. Inflammation impairs the regulation of the colonic motility patterns at several levels, ie, enteric neurons, interstitial cells of Cajal, and circular smooth muscle cells.

GENETIC CRITERIA

IBD may be defined by genetic criteria in several animal species. Crohn's disease and ulcerative colitis are more common in certain human genotypes, and a mutation in the NOD2 gene (nucleotide-binding oligomerization domain2) has been found in a sub-group of patients with Crohn's disease. Genetic influences have not yet been identified in feline IBD, but certain breeds (eg, Siamese) appear to be at increased risk for the disease.

CLINICAL EXAMINATION

The clinical signs of large intestinal IBD are those of a large bowel-type diarrhea, ie, marked increased frequency, reduced fecal volume per defecation, blood pigments and mucous in feces, and tenesmus. Anorexia, weight loss, and vomiting are occasionally reported in cats with severe IBD of the colon or concurrent IBD of the stomach and/or small intestine. Clinical signs usually wax and wane in their severity. A transient response to symptomatic therapy may occur during the initial stages of IBD. As the condition progresses, diarrhea gradually increases in its frequency and intensity, and may become continuous. In some cases the first bowel movement of the day may be normal or nearly normal, whereas successive bowel movements are reduced in volume and progressively more urgent and painful. During severe episodes, mild fever, depression, and anorexia may occur.

Physical examination is unremarkable in most cases. Thickened bowel loops may be detected during abdominal palpation if the small bowel is concurrently involved. Digital examination of the anorecturm may evoke pain or reveal irregular mucosa and blood pigments and mucous may be evident on the exam glove.

DIAGNOSIS

Complete blood counts, serum chemistries, and urinalyses are often normal in mild cases of large bowel IBD. Chronic cases may have one or more subtle abnormalities. One review of canine and feline IBD reported several hematologic abnormalities including mild anemia, leukocytosis, neutrophilia with and without a left shift, eosinophilia, eosinopenia, lymphocytopenia, monocytosis, and basophilia. The same study reported several biochemical abnormalities including increased activities of serum alanine aminotransferase and alkaline phosphatase, hypoalbuminemia, hypoproteinemia, hyperamylasemia, hyperglobulinemia, hypokalemia, hypocholesterolemia, and hyperglycemia. No consistent abnormality in the complete blood count or serum chemistry has been identified.

A scoring index for disease activity in canine and IBD was recently developed that relates severity of clinical signs to serum acute-phase protein (C-reactive protein, serum amyloid A) concentrations. The IBD activity index assigns levels of severity to each of several gastroenterologic signs (eg, anorexia, vomiting, weight loss, diarrhea), and it appears to be a reliable index of mucosal inflammation in IBD. Interestingly, both the activity index and serum concentrations of C-reactive protein (CRP) improve with successful treatment, suggesting that serum CRP is suitable for the laboratory evaluation of therapy in canine IBD. Other acute-phase proteins were less specific than CRP. One important caveat that should be emphasized is that altered CRP is not *prima facie* evidence of gastrointestinal inflammation. Concurrent infections or other inflammatory conditions could cause an acute-phase response, including CRP, in affected patients.

TREATMENT

Dietary Therapy

The precise immunologic mechanisms of feline IBD have not yet been determined, but a prevailing hypothesis for the development of IBD is the loss of immunologic tolerance to the normal bacterial flora or food antigens. Accordingly, dietary modification may prove useful in the management of feline IBD. Several nutritional strategies have been proposed including novel proteins, hydrolyzed diets, anti-oxidant diets, medium chain triglyceride supplementation, low fat diets, modifications in the omega-6/omega-3 (ω-6/ω-3) fatty acid ratio, and fiber supplementation. Of these strategies, some evidence-based medicine has emerged for the use of novel protein, hydrolyzed, and fiber-supplemented diets.

Food sensitivity reactions were suspected or documented in 49% of cats presented because of gastroenterologic problems (with or without concurrent dermatologic problems) in a prospective study of adverse food reactions in cats. Beef, wheat, and corn gluten were the primary ingredients responsible for food sensitivity reactions in that study, and most of the cats responded to the feeding of a chicken- or venison-based selected-protein diet for a minimum of 4 weeks. The authors concluded that adverse reactions to dietary staples are common in cats with chronic gastrointestinal problems and that they can be successfully managed by feeded selected-protein diets. Further support for this concept comes from studies in which gastroenterologic or dermatologic clinical signs were significantly improved by the feeding of novel proteins.

Evidence is accruing that hydrolyzed diets may be useful in the nutritional management of canine IBD. The conceptual basis of the hydrolyzed diet is that oligopeptides are of insufficient size and structure to induce antigen recognition or presentation. In one preliminary study, cats with inflammatory bowel disease showed significant improvement following the feeding of a hydrolyzed diet although they had failed to respond to the feeding of a novel protein. Clinical improvement could not be solely attributed to the hydrolyzed nature of the protein source because the test diet had other modified features, ie, high digestibility, cornstarch rather than intact grains, medium chain triglycerides, and an altered ratio of ω-6 to ω-3 polyunsaturated fatty acids. Additional studies will be required to ascertain the efficacy of this nutritional strategy in the management of IBD.

Antibiotics

Some IBD cases are initiated by true enteric pathogens, while others are complicated by small intestinal bacterial overgrowth. Some IBD cases may show short term responsiveness to one or more antibiotics, eg, tylosin, metronidazole, or oxytetracycline.

Probiotics

Probiotics are living organisms with low or no pathogenicity that exert beneficial effects (eg, stimulation of innate and acquired immunity) on the health of the host. The gram-positive commensal lactic acid bacteria (eg, Lactobacilli) have many beneficial health effects, including enhanced lymphocyte proliferation, innate and acquired immunity, and anti-inflammatory cytokine production. *Lactobacillus rhamnosus* GG, a bacterium used in the production of yogurt, is effective in preventing and treating diarrhea, recurrent *Clostridia difficile* infection, primary rotavirus infection, and atopic dermatitis in humans. *Lactobacillus rhamnosus* GG has been safely colonized in the canine gastrointestinal tract, although probiotic effects in the canine intestine have not been firmly established. The probiotic organism, *Enterococcus faecium* (SF68), has been safely colonized in the canine gastrointestinal tract, and it has been shown to increase fecal IgA content and circulating mature B (CD21+/MHC class II+) cells in young puppies. It has been suggested that this probiotic may be useful in the prevention or treatment of canine gastrointestinal disease. This organism may, however, enhance *Campylobacter jejuni* adhesion and colonization of the dog intestine, perhaps conferring carrier status on colonized dogs. The role and evidence-based medicine in support of probiotic therapy in the colitis form of IBD in cats is inadequately reported.

Anti-Inflammatory/Immunosuppressive Therapy

Metronidazole – Metronidazole (10–20 mg/kg PO BID-TID) has been used in the treatment of mild to moderate cases of large bowel IBD in both dogs and cats. Metronidazole has been used either as a single agent or in conjunction with 5-aminosalicylates or glucocorticoids. Metronidazole is believed to have several beneficial properties, including anti-bacterial, anti-protozoal, and immunomodulatory effects. Side effects include anorexia, hypersalivation, and vomiting at recommended doses and neurotoxicity (ataxia, nystagmus, head title, and seizures) at higher doses. Side effects usually resolve with discontinuation of therapy but diazepam may accelerate recovery of individual patients.

Glucocorticoids – Anti-inflammatory doses of prednisone or prednisolone (1–2 mg/kg PO SID) may be used as adjunctive therapy to dietary modification in feline IBD. Prednisone or prednisolone is used most frequently, as both have short durations of action, are cost-effective, and are widely available. Equipotent doses of dexamethasone are equally effective but may have more deleterious effects on brush border enzyme activity. Prednisone should be used for 2 to 4 weeks depending upon the severity of the clinical signs. Higher doses of prednisone (eg, 2–4 mg/kg PO SID) may be needed to control severe forms of eosinophilic colitis or hypereosinophilic syndrome in cats. Combination therapy with sulfasalazine, metronidazole, or azothioprine may reduce the overall dosage of prednisone needed to achieve remission of clinical signs. As with sulfasalazine, the dose of glucocorticoid may be reduced by 25% at 1- to 2-week intervals while hopefully maintaining remission with dietary modification.

Because of steroid side effects and suppression of the hypothalamic-pituitary-adrenal axis, several alternative glucocorticoids have been developed that have excellent topical (ie, mucosal) anti-inflammatory activity but are significantly metabolized during first pass hepatic metabolism. Budesonide has been used for many years as an inhaled medication for asthma, and an enteric-coated form of the drug is now available for treatment of IBD in humans (and animals).

Cyclosporine – Cyclosporine has been used in the renal transplantation patient for its inhibitory effect on T-cell function. In more recent times, cyclosporine has been used in a number of immune-mediated disorders, including keratoconjunctivitis sicca, perianal fistula (anal furunculosis), and immune-mediated hemolytic anemia (IMHA). Anecdotal reports suggest that cyclosporine (3–7 mg/kg PO BID) may be useful in the treatment of some cases of refractory IBD. Evidence-based medicine studies will be needed to establish efficacy, but anecdotal experience would suggest that cyclosporine may be useful in some of the more difficult or refractory cases of IBD.

Chlorambucil – Chlorambucil (2 mg/m^2 PO every other day) has been used in place of azathioprine in some difficult or refractory cases of feline IBD.

REFERENCE

1. A more detailed review of diseases of the large intestine, including 294 references, may be found in: Washabau RJ. Diseases of the Intestine. In, Textbook of Veterinary Internal Medicine, 6th edition, Ettinger SJ and Feldman EC, editors. WB Saunders Co, Philadelphia, 2005, pp 1378-1408.

VOMITING CATS: WHAT'S NEW FOR AN OLD PROBLEM

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Vomiting is a common and frequently complex problem in cats. Adult cats often have different and more chronic causes of vomiting than kittens, but the condition remains a common reason for cats to be presented to veterinarians for care. Vomiting can be caused by both primary gastrointestinal diseases (eg, infectious, inflammatory, parasitic, anatomic (obstructive, trichobezoars), drug-related or nutritional) and by extra-gastrointestinal (GI) diseases, such as endocrinopathies (eg, hyperthyroidism), metabolic disease (eg, renal failure), inflammatory or other liver diseases, pancreatitis, and neoplasia (especially alimentary lymphoma). This wide spectrum of potential causes of vomiting in cats increases the difficulty for the practitioner in making a definitive diagnosis. Nevertheless, it is important to carefully consider each of the potential differentials to prevent the problem from progressing to create further clinical deterioration.

The purpose of this article is not to present a comprehensive review of all causes of vomiting, but to provide an overview of some of the more common causes of vomiting in cats, and to discuss the best approaches for diagnosis and treatment of these different problems. Where appropriate, the role of diet in both diagnosis and therapy of vomiting will also be considered.

EXTRA-GASTROINTESTINAL CAUSES OF VOMITING

One of the first steps in evaluating a vomiting cat is to attempt to determine as quickly as possible, whether the vomiting is due to a primary gastrointestinal problem (eg, gastritis, inflammatory bowel disease [IBD]), or caused by a disease outside of the gastrointestinal tract (eg, liver or renal disease, pancreatitis, endocrinopathies, heartworm). In many cases of vomiting due to gastrointestinal disease, the diagnosis is made by imaging, evaluation of tests of GI function, or biopsy of the GI tract. However, in extra-GI causes of vomiting, laboratory tests are more important to determining the cause of the problem (eg, thyroxine levels for hyperthyroidism, chemistry panel for renal or liver disease). The best way to help point the clinician toward the proper diagnostic approach is to obtain a thorough history of the problem and perform a complete physical examination. These tools of the medical trade are often underestimated in their importance, but can be invaluable to the clinician in helping to refine and focus the diagnostic approach.

Feline Pancreatitis

Feline pancreatitis is a very difficult disease to definitively diagnose ante mortem (especially chronic cases or in cats that only vomiting occasionally or intermittently). This partly due to the lack of specific clinical signs in cats, as well as the lack of a rapidly available test for diagnosis of the disease. In cats with chronic pancreatitis, the available tests are even less sensitive and specific, thus diagnosis is even more very difficult.

The clinical signs of feline pancreatitis can be quite different from those in dogs. Acute pancreatitis is frequently encountered in obese dogs fed a high-fat diet, while cats are more likely to be underweight, and high-fat diets do not appear to be an important predisposing factor. Cats of all ages, sexes, and breeds are affected, although Siamese cats are reported to have pancreatitis more frequently. Finally, the clinical signs of pancreatitis in cats are very vague, with the most common signs being lethargy (reported in 100% of cats in one study), anorexia, dehydration and abnormal body temperature (either fever or hypothermia can be observed). Vomiting and anterior abdominal pain, which are common clinical signs in dogs with acute pancreatitis, occur in only 35% and 25% of cats, respectively. Cats with severe necrotizing pancreatitis may be icteric or in shock and may have other concurrent conditions, including hepatic lipidosis, cholangiohepatitis, inflammatory bowel disease, interstitial nephritis, diabetes mellitus or vitamin K-responsive coagulopathy. Thus, the clinical signs may be quite variable, and this must be taken into consideration with each patient.

Routine evaluation of vomiting cats with suspected pancreatitis (or other extra-GI causes of vomiting) may include hematology, a serum biochemistry profile, urinalysis, abdominal radiography and/or ultrasound, and serum assays of pancreatic function (eg, feline trypsin like immunoreactivity [fTLI], or feline pancreatic lipase immunoreactivity [fPLI]). If appropriate, tests for hyperthyroidism, liver function, or other specific tests may be indicated. Hematologic findings in cats with pancreatitis are nonspecific, but may include a nonregenerative anemia, leukocytosis or leukopenia (less common). In a recent study, cats with pancreatitis consistently had an elevated WBC (20,300 cell/μL) and mild decreases in platelets (mean = 180,000 platelets/μL). Reported changes in the serum chemistry profile include elevated serum alanine aminotransferase (ALT), elevated serum alkaline phosphatase (ALP), hyperbilirubinemia, hyper- or hypoholesterolemia, hyperglycemia, azotemia, and hypokalemia. In a recent study, the most common abnormalities in cats with severe pancreatitis were hyperglycemia (180 mg/dL), hyperbilirubinemia (2.5 mg/dL), hypocholesterolemia (130 mg/dL), and hypoalbuminemia (1.8 g/dL). Liver enzyme elevations were more common in cats with mild pancreatitis (determined by surgical biopsy), and gamma-glutamyltransferase (GGT), ALP, and ALT were all moderately elevated in these cats. Hypocalcemia is less commonly observed, but when present may be a poor prognostic sign seen in cats with severe pancreatitis or multiple organ dysfunction. Serum lipase may be increased early in acute pancreatitis, but in a recent study amylase and lipase were found to be of little diagnostic value in distinguishing normal cats from those with pancreatitis. There are no changes in the urinalysis consistently observed or specific for pancreatitis in cats.

The fTLI was developed years ago as the definitive test for diagnosis of exocrine pancreatic insufficiency, and the data and follow-up have confirmed its utility for this condition. In recent years, others have evaluated the fTLI as a diagnostic test for acute pancreatitis, working on the premise than an elevation in serum concentrations was consistent with pancreatic leakage or inflammation. While an increase in fTLI can be found in cats with acute pancreatitis, a normal fTLI does not rule out pancreatitis. This is because the leakage of enzymes tends to decrease rapidly following an event, or the enzymes are inactivated and scavenged by the body's peptidases (macroglobulin, etc.) within 12 to 24 hours following an acute insult. Further, in chronic or low-grade pancreatitis, the leakage is not great enough to be detected by this assay. Thus, while an increase in fTLI is specific for pancreatic enzyme leakage, it is not sensitive enough to be a definitive test for pancreatitis. More recently, an ELISA for pancreatic specific lipase (feline pancreatic lipase immunoreactivity, fPLI) was developed by the GI lab at Texas A&M University. The assay is species specific, has been used to detect elevations in pancreatic lipase in clinical cases, and appeared to be more specific and sensitive for diagnosis of pancreatitis in cats than fTLI. However, the assay had a relatively low sensitivity (33%) and specificity (<80%) when a cut-off value of 100 µg/L was used for diagnosis. To improve upon this assay, a radioimmunoassay (RIA) was developed and validated in 30 healthy cats. In a recent paper, the sensitivity and specificity of this assay was tested in cats with mild pancreatitis and in cats with moderate to severe pancreatitis. The sensitivity in mild pancreatitis was found to be 80% while the specificity in healthy cats 75%. However, in severe pancreatitis (determined by pancreatic biopsy) the sensitivity and specificity were both 100%. These findings underscore the utility of this test in cats with acute pancreatitis; however, there still is a problem with detection of low-grade or chronic pancreatic inflammation in cats with this assay. In cats with chronic pancreatitis, it will still be necessary to evaluate the combined historical, physical exam, lab data and imaging information along with the fPLI when making a diagnosis.

Imaging studies are frequently used to help identify cats with acute pancreatitis; however, the changes are not consistent and can be particularly subject to interpretation and operator expertise. The most common radiographic abnormalities include a generalized or focal (upper right quadrant) loss of peritoneal detail (suggesting peritonitis or peritoneal effusion), presence of a mass in the area of the pancreas, hepatomegaly, dilated intestinal loops, or a fluid-filled duodenum. However, these findings are not specific for pancreatitis, and the sensitivity of radiography for diagnosing pancreatitis is low in cats. Ultrasonography may reveal a hypoechoic pancreas, hyperechoic mesentery, a mass effect, a dilated common bile duct or it may be normal. In previous studies, the sensitivity of ultrasound for diagnosis of pancreatitis was reported to be 24%. In a recent study, mild pancreatitis was still shown to be difficult to diagnose via abdominal ultrasound. However, in that same study, ultrasound had an 80% sensitivity and 88% specificity in cats with moderate to severe pancreatitis. The most reliable method for making an accurate diagnosis of pancreatic disease remains direct visualization and histopathology. However, this can be expensive, increase the risk of complications (anesthesia/surgery), and in cases with focal lesions, which is common with chronic pancreatitis, the lesions may be missed on visual or histopathologic inspection.

Feline Liver Diseases (Cholangitis, Idiopathic Hepatic Lipidosis)

Diseases affecting the liver are a common clinical problem in cats. There are four major types of liver disease in cats: hepatic lipidosis, cholangiohepatitis complex, infectious hepatitis (eg, FIP), and neoplastic liver disease (eg, lymphoma). As with all diseases of the liver, histopathology is required for a definitive diagnosis, and this is the most important step in determining treatment and prognosis. Nevertheless, once a diagnosis is obtained, the goal for treatment of cats with severe liver disease is to provide optimal nutritional and pharmacologic support to maximize liver function, minimize future liver damage or scarring, and to control the concurrent clinical signs such as vomiting, to promote a high quality of life.

Inflammatory, infectious, or metabolic liver disease can present in cats with few external clinical signs other than inappetance, vomiting, or lethargy, or can cause severe illness resulting in development of ascites, icterus, hepatoencephalopathy, coagulopathy, and loss of ability to appropriately metabolize protein or carbohydrates. Thus, there is no single set of clinical signs or laboratory abnormalities that will define all liver disease patients. Nevertheless, there are some important clues that can help guide the clinician through to a definitive diagnosis.

Key Diagnostic Features in Feline Liver Disease

- In cats, the half-life of both serum ALP and ALT enzymes are much shorter than in dogs, so any elevation of these enzymes should be considered significant. As in dogs, neither the ALP or ALT is specific for a type of liver disease or representative of the degree of liver damage or functionality; however, elevations of these enzymes provide evidence that further evaluation is indicated.
- Serum GGT is a more specific, and sensitive test of biliary tract disease in cats, and thus, is often increased in cats with cholangiohepatitis but is usually not increased in cats with idiopathic feline hepatic lipidosis.
- In addition to liver enzyme activities, there are five key parameters to assess in a cat with suspected liver disease: albumin, total bilirubin, glucose, BUN, and cholesterol. All of these have important ties to liver function and be very useful clinical clues to the severity of the illness. Further liver function testing (eg, bile acid testing) is not needed in cats with

hyperbilirubinemia not due to extra-hepatic causes, as this confirms the presence of liver dysfunction.

- Icterus may indicate liver disease, but the key is to remember that hyperbilirubinemia may occur due to PREHEPATIC (hemolytic), HEPATIC, or POSTHEPATIC (biliary tree, gallbladder, and common duct) causes. All three types of cholangiohepatitis can be associated with icterus, so this is not a good sign to distinguish them.
- Ascites can also indicate liver disease, but it too, can have prehepatic (cardiac), hepatic, or post-hepatic (portal hypertension, portal vein thrombosis, GI disease). Further, leakage of fluid into third spaces can be from leaky vessels (vasculitis), lack of colloid oncotic pressure (low albumin), or increased intravenous pressure (cardiovascular, thromboembolic disease). In general, ascites is a rare finding in cats with inflammatory liver diseases, unless the disease is chronic enough to cause fibrosis and portal hypertension.
- The liver is the major site of synthesis of most coagulation factors, coagulation inhibitors, and other essential elements of the clotting system; thus, it is highly advisable to assess a buccal mucosal bleeding time, prothrombin time, and platelet count prior to performing a liver aspirate or biopsy. However, a recent study showed that cats with significant liver disease and coagulopathy may still have normal prothrombin times, and in these cats the PIVKA test and BMBT may be more reliable. Vitamin K therapy prior to surgery or biopsy is recommended in all cats with severe liver disease.
- Analysis of the liver via imaging is an important method of assessing liver size (eg, chronicity), liver echogenicity (eg, circulation, biliary tree, infiltrative or space occupying diseases), and the presence of other abnormalities, such as masses, gallstones, bile duct obstruction, etc.
- Despite all of these approaches, liver disease is defined and classified on the basis of histomorphologic appearance. In other words: biopsy is essential to defining the problem and making an appropriate plan for treatment.
- Whenever liver tissue is obtained for biopsy, additional tissue should be collected for culture, especially in cats with fever, acute onset of signs, or when acute (suppurative) cholangiohepatitis is suspected.

Ultimately, for appropriate therapy to be instituted, a definitive diagnosis must be obtained; however, supportive therapy is also important in cats with liver disease. The most commonly used hepatosupportive therapy is SAMe (S-adenosylmethionine), which has been shown to increase hepatic levels of glutathione, an important free radical scavenger and antioxidant.

There are a number of other important extra-GI causes of vomiting to consider, including feline hyperthyroidism, chronic renal disease, endocrinopathies such as addisons or diabetic ketoacidosis, and other systemic diseases such as heartworm disease. A complete discussion of each of these subjects is not possible here, but the reader is reminded to consider these possibilities when confronted with vomiting cats for which a definitive diagnosis is not yet made.

PRIMARY GASTROINTESTINAL CAUSES OF VOMITING

Adverse Reactions to Food

Food sensitivity and food intolerance are the most common adverse reactions to food in cats. Food allergy or hypersensitivity is an adverse reaction to a food or food additive with a proven immunologic basis. Food intolerance is a non-immunologic, abnormal physiologic response to a food or food additive. Both can be responsible for diarrhea or vomiting, but vomiting is a more common presenting complaint. Food poisoning, food idiosyncrasy, and pharmacologic reactions to foods also come under this category of adverse reactions to food. The specific food allergens that cause problems in cats have been poorly documented, with only 10 studies describing the clinical lesions associated with adverse food reactions. In these reports, over 80% of the reported cases were attributed to beef, dairy products, or fish in cats. The incidence of food allergy versus food intolerance in cats is unknown. However, a recent study by Guilford and associates suggested that 33% of cats with vomiting or other GI signs had food sensitivity. The diagnosis of both food sensitivity and intolerance is based upon a dietary elimination trial. The major difference between these two types of adverse food reactions is the length of time on the diet that is required to achieve a response (cats with food sensitivity require 6 to 12 weeks on the elimination diet before an improvement will be seen). Alternatively, in cats with food intolerance, resolution of signs usually occurs within days of the diet change (unless there is concurrent bacterial floral disruption or other factors influencing the response). There are a variety of commercially available and homemade elimination diets, as well as diets formulated with hydrolyzed proteins, that may be used in cats with suspected food sensitivity or intolerance. The key is to select a diet that has a novel or hydrolyzed protein source (based on a careful dietary history), that is balanced and nutritionally adequate (commercial diets are best for this), however, homemade elimination diets may be needed to find an appropriate test diet. If a homemade diet must be used for long-term therapy, a complete and balanced diet containing the necessary protein sources should be formulated by a nutritionist. In most cats with food sensitivity, avoiding the offending food is the most effective therapy and will result in complete resolution of signs. However, short-term steroid therapy can be used to decrease the concurrent intestinal inflammation until the appropriate food sources can be identified.

Finally, some cats with vomiting due to food related causes will respond to placing them on a high protein, low carbohydrate diet (canned growth or diabetic formula foods). The reason why kittens or cats respond to these diets is not completely known, but may be related to carbohydrate intolerance or to changes in the bacterial flora that result from some foods. While this hypothesis remains to be proven in cats, there is increasing anecdotal evidence that in cats with signs of GI disease such as vomiting, feeding a canned diet containing either highly digestible moderate carbohydrate or high protein and low carbohydrate content is beneficial. Obviously, dietary therapy is not the answer to effective control in all vomiting cats, but in many of these cats dietary therapy is an important component of therapy that should be carefully considered and implemented, and adjusted to meet the needs of the pet and its situation.

The use of diet to assist in the management of vomiting is not a new concept. Nevertheless, the type of diet used to help manage the problem has become an increasingly complex issue. In many, if not most cases of uncomplicated vomiting or vomiting due to food type, the best approach is to feed a highly digestible diet or change the diet to one with fewer additives, flavorings, or other substances than may be associated with food intolerance. These types of diets are designed to provide food that is easy to digest (moderate to low fat, moderate protein, moderate carbohydrate), may have additives to improve intestinal health (soluble fibers, omega-3 fatty acids, increased anti-oxidant vitamins, etc), and contain no gluten, lactose, food coloring, preservatives, and so forth. There are many different brands available that fall under the category "highly digestible," but, the key is to remember that they are not all alike. Thus, when one diet from this category not accepted by the cat, is ineffective, or seems to make the problem worse, you cannot assume that all diets in this category will be ineffective. The highly digestible diets from different pet food manufacturers have a wide variety of different formulations: different protein and carbohydrate sources, different levels of fat, and a variety of additives designed to promote intestinal health (FOS, MOS, omega-3 fatty acids, antioxidant vitamins, soluble fiber, etc.). If one type of highly digestible diet has been fed for at least 2 weeks with minimal response, then is it entirely reasonable to either try another diet from a different source, or try an entirely different dietary strategy (eg, high protein/low carb, novel antigen, hydrolyzed). Another consideration is that the cat may improve by taking into account the amount or type of food fed. For example, feeding a canned food diet may improve gastric emptying—especially if the vomiting is occurring immediately after eating. Alternatively, if canned food is not an option, feeding smaller meals more frequently, to reduce vomiting that occurs in cats with altered gastric motility or reflux. The key is to remember that dietary management is a trial and error process—there is no single diet that will benefit all cats in all situations.

INFLAMMATORY OR IMMUNE-MEDIATED CAUSES OF VOMITING

Inflammatory bowel disease (IBD) in cats is a commonly diagnosed condition of adult cats that may represent multiple etiologies. IBD is characterized by persistent clinical signs (vomiting, diarrhea or weight loss) consistent with GI disease that occur in the absence of an identifiable cause but also have histologic evidence of mucosal inflammation and structural changes. There are a number of possible causes of intestinal inflammation that must be considered in the diagnostic process, including infectious, food sensitivity/intolerance, hyperthyroidism, neoplastic, or protozoal and parasitic. These should be investigated thoroughly or empirical therapy instituted prior to settling on the diagnosis of idiopathic IBD. Food sensitivity can be particularly difficult to distinguish from IBD or other intestinal disorders. In a recent study, food sensitivity was reportedly responsible for at least 30% of all feline GI problems. Thus, appropriate food trials are an extremely important component of both diagnosis and therapy of cats with GI disease or suspected IBD. In addition to food trials, the diagnostic plan for a cat with chronic diarrhea should include multiple fecal examinations or therapeutic deworming, assessment of thyroid and FeLV/FIV status, and intestinal vitamin (cobalamin) status. Serum cobalamin levels in cats commonly decrease with severe distal bowel disease, and in cats with hypocobalaminemia, the diarrhea will not resolve until replacement therapy is instituted. Cobalamin therapy (250 µg/cat IM q week) in some cats may be lifelong, while in others, once the clinical disease resolves the supplementation can be discontinued. In addition, radiographs and ultrasound are important in assessment for the presence of infiltrative diseases such as FIP granulomas, histoplasmosis or lymphosarcoma. But, ultimately, intestinal biopsies, either obtained endoscopically or at an exploratory surgery are essential—both for the diagnosis of IBD and for ruling out other specific causes of the clinical signs. In humans, recent studies indicate a strong association of development of IBD with a breakdown of normal tolerance mechanisms, host susceptibility and the enteric microflora. It is quite likely that these same factors are important in feline IBD, and in studies using experimental models of IBD, the resident microflora are essential cofactors in driving the inflammatory response. Further, modulation of the enteric microenvironment in humans with IBD has been shown to reduce proinflammatory cytokines in the mucosa and thus, decreases the inflammation. Unfortunately, accurate, readily accessible methods of assessing the bacterial numbers and species populating the small intestine are not yet available. In addition, studies in cats with IBD assessing modulation of the enteric flora (using probiotics, prebiotics, or other specific therapy for cytokines) are only in the early stages of study. At this time, therapy of IBD in cats continues to include inflammatory suppression and antibiotic therapy. The most effective therapies for IBD include steroids (prednisolone or methylprednisolone 1–2 mg/kg PO q12h) or other drugs that interrupt the pro-inflammatory pathways that are active in the gut. In cats that are intolerant of steroids, or in those in which steroids are no longer effective, immunosuppressive therapy may be necessary, and is often effective. Antibiotic therapy with metronidazole (5–10 mg/kg PO q12h) or tylosin

(5–15 mg/kg q12h) has been effectively used for control of bacterial associated disease and continues to be recommended for initial therapy of IBD. Whether this is due to the antibiotic effects of these drugs and their influence on the intestinal microflora or due to their immune-modulating activities is unknown, but nevertheless therapy with these drugs continues to be helpful. Caution is advised in using these drugs on a continuous or chronic basis, and if needed they should be used intermittently, not continuously. Finally, general agreement exists among gastroenterologists that elimination diets or novel protein, highly digestible diets are beneficial in cats with IBD. Nevertheless, agreement also exists that dietary management alone is seldom successful, thus control of the aberrant inflammatory process and bacterial components are still necessary. Further, at this point in our understanding, we still do not know which components of the diet (protein, carbohydrate, minerals, etc) are important in the pathogenesis or therapy of IBD, or if other aspects of nutritional support (fatty acids, probiotics or other nutriceutical therapy) may reduce the inflammatory response. There is increasing data in human IBD that probiotics and antioxidant, prebiotic nutraceuticals may be important components of therapy.

NONSPECIFIC THERAPY OF VOMITING

There are a number of antiemetic agents available for use in cats that are vomiting. Some are more commonly used in the hospital setting because they are injectable and may require frequent administration. The α_2-adrenergic antagonists (phenothiazines) and 5-HT_3 antagonists (ondansetron) appear to be the most effective antiemetic agents in the cat. Cats may be treated with chlorpromazine (α_2-adrenergic antagonist) at a dose of 0.2–0.4 mg/kg administered subcutaneously or intramuscularly every 8 hours, or with any of the 5-HT_3 antagonists (ondansetron 0.1–1.0 mg/kg, granisetron 0.1–0.5 mg/kg, or dolasetron 0.5–1.0 mg/kg, orally or intravenously every 12 to 24 hours). Dopaminergic antagonists, eg, metoclopramide, are less effective antiemetic agents in the cat, and because they antagonize dopamine, may potentially reduce pancreatic blood flow (this effect has not been proven in cats with pancreatitis). However, this drug is available in an oral preparation that can be used for therapy at home. While nonspecific therapy may be indicated to control vomiting, it is important to remember that finding the cause of vomiting is important, rather than just controlling the clinical sign. Thus, antiemetic therapy should be used judiciously in the clinical setting and as an adjunct to therapy for the primary problem.

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A CLINICAL APPROACH TO THE BLEEDING PATIENT

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Several in-practice diagnostic tests are available to simply reach a specific diagnosis of bleeding disorders. These include thrombocytopenias, thrombocytopathias, von Willebrand disease and many coagulopathies including DIC. The practical approach utilizing signalment, history, clinical signs, and diagnostic in-practice and laboratory tools will be reviewed and illustrated with specific clinical case examples.

Bleeding diatheses are generally separated into primary and secondary hemostatic disorders and in some cases both systems are affected such as in disseminated intravascular coagulation (DIC). Primary hemostatic disorders include not only the common thrombocytopenias but also thrombopathias, vasculopathies, and von Willebrand disease. Secondary hemostatic disorders include all coagulation factor deficiencies involved in fibrin formation. Platelet and vascular problems often present with surface hemorrhage while coagulopathies generally cause hematomas and cavity bleeds. Excessive hemorrhage at an injury or surgery site and bleeding from multiple places are suggestive of bleeding disorder and there are a few breed predilections for specific hereditary defects.

Hemostatic tests are indicated whenever an animal is bleeding excessively, prior to surgery when an increased bleeding tendency is suspected, to monitor therapeutic interventions, and for genetic screening in certain breeds or families with a known bleeding disorder. Hemostatic abnormalities should be assessed prior to instituting therapy whenever possible or at least appropriate blood samples should be collected pretreatment. Excellent venipuncture with discarding of the first few drops of blood (to avoid platelet activation and tissue factor) and extended compression over jugular, saphenous or femoral vein is required. The cuticle bleeding time crudely assesses overall hemostasis, but is not standardized and painful and is, therefore, not recommended. A minimal database includes a packed cell volume and total protein evaluation. Evaluation of a blood smear can provide a platelet estimate and identify platelet size and clumping as well as schistocytes. The results can provide some measure of the extent of blood loss and red blood cell transfusion requirement.

TESTS FOR PRIMARY HAEMOSTATIC DEFECTS

Platelet counts can be estimated on a blood smear or specifically counted by a hematology instrument. Since 8–15 platelets (1 platelet equals 20,000/μL) are normally found per high power oil emersion microscopic field, an absence to low number of platelets suggests a severe thrombocytopenia. Various modern impedance and laser hematology instruments have the ability to count platelets and measure their mean size including platelet size distribution; they may have been validated, but some have difficulties in differentiating large platelets from erythrocytes particularly in cats. Furthermore, canine platelets can readily be activated which results in platelet aggregation; hence, platelet counts need to be confirmed by a careful review of a blood smear including the feather edge for platelet clumps. Hemorrhage is generally not observed unless the platelet count is <40,000/μL (normal 150–500,000/ μL).

Thrombocytopenia, a common cause of surface hemorrhage in dogs, can result from impaired thrombopoiesis, increased platelet destruction and consumption, and sequestration of platelets (splenomegaly). Reduced platelet production may be isolated or associated with an overall decreased hematopoiesis due to many drug reactions (estrogens, chemotherapeutics, azathioprine), infections (*Ehrlichia* spp), and myelophthisis (leukemia, myeloma, myelofibrosis) but remains often idiopathic (immune-mediated?). Accelerated platelet destruction is commonly associated with immune-mediated thrombocytopenia (IMT), but enhanced platelet consumption may also be observed with neoplasia, vasculitis, and disseminated intravascular coagulation (DIC). IMT can be divided into primary, also known as idiopathic thrombocytopenia purpura (ITP), and secondary forms triggered by infections (*Ehrlichia, Rickettsia*, and *Babesia* spp, *Anaplasma* spp, vaccines), drugs, and cancer. Anticoagulant rodenticide poisoning can also be associated with mild to moderate thrombocytopenia. However, acute and chronic blood loss does not result in any significant consumptive thrombocytopenia unless there is concomitantly a vasculopathy or DIC present. Because thrombocytopenia occurs rarely in cats and is generally associated with drug exposure (griseofulvin, methimazole, propylthiouracil), viral infections, or malignant diseases, it will not be further discussed here.

A diagnosis of thrombocytopenia is made by a platelet estimate on a blood smear or complete blood cell count, but any thrombocytopenia must be verified by a review of a blood smear. Spurious thrombocytopenia may due to instrument limitations: For example, megaplatelets in Cavalier King Charles Spaniels; platelet aggregates with many illnesses and collection techniques; and a generally mild thrombocytopenia in Greyhounds. Classic signs of thrombocytopenia include petechiation, ecchymosis, epistaxis, and gastrointestinal blood loss. The most severe thrombocytopenias, seen with IMT/ITP, often cause only mild hemorrhage. Following a careful history, a search for an underlying cause is warranted to identify an infection (blood smear, serology, polymerase chain reaction [PCR]) or cancer (also involving lymph nodes and spleen). Bone marrow examination is safe, but may rarely reveal a specific cause on initial presentation. A diagnosis of ITP is mostly based upon excluding other causes of thrombocytopenia, but platelet-associated antibodies can also be determined to support an immune mechanism for thrombocytopenia.

Detection of platelet-associated antibodies further supports an immune-mediated thrombocytopenia, but this test is rarely available. Serum titer, antigen and PCR tests for tick-borne (ehrlichiosis, babesiosis, Rocky Mountain spotted fever) and other infectious diseases are indicated in certain countries or areas. The presence of schistocytes and thrombocytopenia suggests intravascular disseminated coagulation, where intravascular fibrin strands fragment erythrocytes. Because von Willebrand disease is such a common mild primary hemostatic defect in dogs, plasma vWF measurements by ELISA through a commercial laboratory are indicated. For breeding purposes, DNA testing is available for some canine breeds. Finally, in light of normal platelet count and plasma vWF values, a prolonged buccal mucosal bleeding time (BMBT) indicates a thrombopathia. Disposable devices are available that facilitate making one to two standard 1-mm-deep mucosal incisions. The platelet function analyzer (PFA100) is a simple tool to functionally assess primary hemostasis. Electron microscopic and platelet aggregation and nucleotide studies allow further characterization of platelet dysfunctions in specialized laboratories.

COAGULATION TESTS

Whereas the whole blood clotting time test is insensitive, painful, and mostly inaccurate, there are several standardized coagulation screening tests that are useful to define coagulopathies in clinical practice. Nearly all coagulation tests assess the function of certain parts of the coagulation system in fresh whole blood or fresh (or frozen) plasma to generate fibrin in a fibrometer; recalcified citrated plasma is used and many tests are comparing a patient sample directly with a simultaneously obtained control or pool plasma (plasma from 10 animals). Generally coagulation times, measuring the time to clotting (fibrin formation), are much shorter in small animals than in humans; thus, every coagulation test needs to be run on an instrument for animals and validated for the animal species.

The intrinsic and common pathways are assessed by either the activated coagulation time (ACT) or activated partial thromboplastin time (aPTT). Factor XII of the intrinsic cascade is activated by diatomaceous earth (celite) in the ACT test and by kaolin or other contact phase substrates in the aPTT test. The extrinsic and common pathways can be assessed by either the prothrombin time (PT) or the protein induced by vitamin K antagonism or absence (PIVKA) test. Different tissue factors (thromboplastins) are activating factor VII, which in turn will lead to fibrin formation. It should be noted that the PIVKA test is not specific for the detection of anticoagulant rodenticide poisoning, but detects any coagulation factor deficiency of the extrinsic and common pathway and does not add information to the generally run PT test. Until recently, the ACT tube test was the only point-of-care test available for clinical practice, whereas PTT and PT tests were performed in commercial laboratories. There are now new point-of-care coagulation instruments (eg, IDEXX Coag DX, an upgrade from SCA2000) introduced that are capable of determining without delay on small amounts (50 µL) of fresh citrated whole blood the aPTT and PT, thereby making the chilling, rapid separation of citrated plasma and shipment of frozen plasma on dry ice to the laboratory for initial coagulation screening unnecessary. In practice, a reasonable and simple approach for a bleeding animal to be screened for a coagulopathy would be to measure the ACT or aPTT first as either test detects all coagulopathies (except for hereditary factor VII deficiency in Beagles), but the aPTT is more standardized and can be run on fresh whole blood. If the PTT (or ACT) is prolonged, a PT test would be indicated to differentiate between an intrinsic and common pathway defect or a combined coagulopathy involving several coagulation factors.

Although hereditary coagulopathies can be suspected based upon the pattern of coagulation test abnormalities, specific factor analyses are needed to confirm a diagnosis. A bleeding male animal with a prolonged aPTT and normal PT likely has hemophilia A or B (factor VIII or IX deficiency), an X-chromosomal recessive disorder. However, factor XI deficiency is associated with the same test abnormalities and is inherited by an autosomal recessive trait (eg, Kerry blue terriers). Finally, factor XII deficiency, particularly common in domestic shorthair cats, and prekallikrein deficiency causes marked aPTT prolongations but no excessive bleeding tendency. Rodenticide-poisoned animals that are bleeding or are at risk for bleeding will have prolongations in all of the above coagulation tests, but would have a normal thrombin time (TT). The thrombin time is independent of vitamin K-dependent coagulation factors and is a functional assay for fibrinogen to form fibrin. The PIVKA test is not diagnostic, but a toxicologic investigation (product identification, blood toxicology analysis) may confirm the rodenticide poisoning. Moderate thrombocytopenia may be associated with rodenticide poisoning. All liver diseases may result in varied coagulopathies due to impaired coagulation factor synthesis and vitamin K malabsorption. Similarly, disseminated intravascular coagulopathies (DIC), due to many different disorders are associated with variably prolonged coagulation times. More helpful to the diagnosis of DIC are the recognition of schistocytes, thrombocytopenia, low antithrombin III levels, and increased D-dimers and fibrin split (degradation) products. Finally, thromboelastography (TEG or ROTEM) techniques have been improved and can now be used in referral centers to assess overall hemostasis and thrombotic tendencies of citrated whole blood or plasma.

ADVANCES IN LIVER DISEASE TESTING

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Biochemical screening tests facilitated by convenient automated analyzers are used for routine health assessments. Liver disease is often first recognized on the basis of routinely measured liver enzymes. While liver enzymes are sometimes referred to as "liver function tests," they reflect hepatocyte membrane integrity, hepatocyte or biliary epithelial necrosis, cholestasis or induction phenomenon rather than liver functional capacity. Useful enzyme interpretation requires an integrated consideration of a patient's data base: history, physical examination, other laboratory tests, liver function assessment, and imaging studies. In a general population, increased liver enzymes are considerably more common than the prevalence of liver disease. This reflects the influence of systemic disorders on the liver as a result of its sentinel position between the alimentary canal and systemic circulation, and wide exposure to toxins and drug metabolites, endotoxins, and infectious agents (dual blood supply). Consequently, a wide spectrum of nonhepatic disorders influences liver enzyme activity. Certain disorders have "classic" enzyme changes (see Figures 1, 2, 3, and 4).

DEFINITIVE DIAGNOSIS

Confirmation of a specific liver disease *usually* requires liver biopsy. Early detection of chronic necroinflammatory hepatitis often results from recognition of persistent unexplained high serum liver enzyme activity in the absence impaired hepatic function. In dogs, endogenous or exogenous exposure to steroid hormones induces a vacuolar hepatopathy associated with a glucocorticoid alkaline phosphatase (ALP) isoenzyme (this induced ALP has low diagnostic value). However, in many cases, impaired liver function (commonly marked by increased total serum bile acid [TSBA] concentrations) prioritizes biopsy collection. In general, the development of hyperbilirubinemia is a late phenomenon in chronic hepatitis in both the dog and cat. Certain disorders may be recognized on the basis of imaging studies, particularly ultrasonography (US): eg, biliary mucocele, major bile duct obstruction, cholelithiasis, neoplastic nodules (target lesions), and hepatic lipidosis. Several of these disorders may be confirmed after evaluation of a cytologic specimen collected with US guidance and consideration of the clinicopathologic features: eg, hepatic lipidosis, focal neoplasia.

DIAGNOSTIC TEST PERFORMANCE

Performance of a *diagnostic test* depends on disease prevalence. With that in mind, "preliminary studies" of unique "new" tests evaluated in small selected patient populations must be cautiously interpreted. A large appropriate group of animals that reasonably represent the spectrum of disorders confronting a clinician *must be investigated* (that means inclusion of truly affected animals as well as animals thought to have the disorder but later proven to be unaffected). The group of "non-diseased" animals must be adequate in size to permit relevant conclusions. Otherwise, test evaluation is directed as a *screening test*. High specificity (SP) is important for a diagnostic test as this represents the likelihood of a negative test in patients lacking the disorder otherwise hard to discriminate. A "perfect" test for liver disease: 1) has good sensitivity (SS, high ability to detect affected individuals) but should not detect disease before it is histologically classifiable, 2) is minimally influenced by extrahepatic disorders, 3) is both convenient and safe, 4) is affordable, 5) is easy to interpret, 6) is easy to assay with analyses widely available (not restricted to a few specialized laboratories), and 7) has a short turn around time (optimally, one day).

DYNAMIC OR METABOLIC TESTS

Knowledge that the liver removes a large number of substances from its circulation for subsequent metabolism or excretion has generated "dynamic or metabolic" tests of liver function involving a xenobiotic or substrate "probe" metabolized or eliminated by the liver (measurement of it or it's metabolite(s)). Metabolic tests can provide information regarding different physiological and pathologic pathways, depending on the location of the rate-determining enzyme and the influence of hepatic perfusion on substrate or product distribution/elimination. Caution is warranted in applying dynamic metabolic tests in dogs since this species is notoriously susceptible to hepatic enzyme induction (eg, phenobarbital, glucocorticoids, other steroid hormones, NSAIDs, other medications). Dynamic metabolic tests estimate hepatic metabolism or elimination capability for the agent examined. Results *reflect the concept of "hepatic functional mass" as interpreted by the "intact hepatocyte hypothesis" in diseased tissue,* discussed next.

INTACT HEPATOCYTE HYPOTHESIS

The "intact hepatocyte hypothesis" maintains that hepatocyte function is preserved in chronic liver disease, with diminution in hepatocyte number and development of functional (anatomic and kinetic) shunts responsible for apparent alterations in liver function. Acquired microcirculatory "hepatic shunting" impair exchange between hepatocytes and sinusoidal blood, contributing to liver failure irrespective of the metabolic capacity of hepatocytes. In chronic disease, this is associated with transformation of hepatic sinusoids (normally having discontinuous capillaries [many fenestrations]) into continuous capillaries lacking the ample dynamic sinusoidal fenestrae that normally facilitate substrate diffusion into the space of Disse. Development of hepatic fibrosis predictably increases intrahepatic portal venous resistance increasing portal pressure even at low flow rates, favoring development of acquired splanchnic portosystemic shunts (in the abdominal cavity). Intrahepatic "microvascular" shunting between portal and

Figure 1. Dogs: Two toxins, surgical shunt creation.

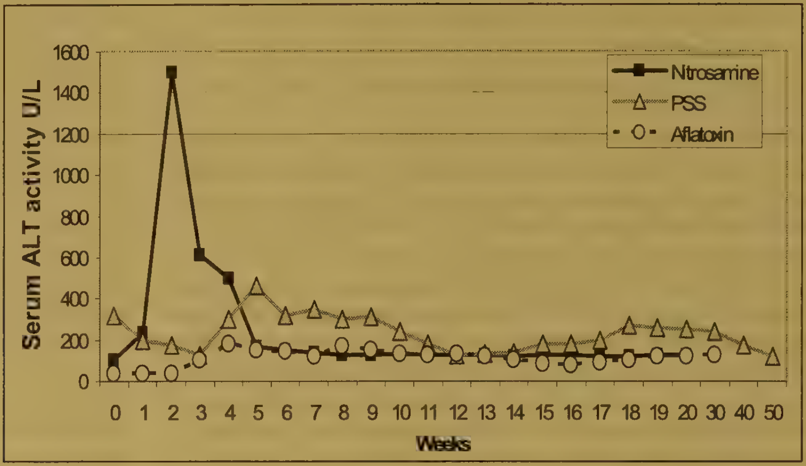


Figure 2. Dogs receiving (gray box) Prednisone 4.4 mg/kg/day.

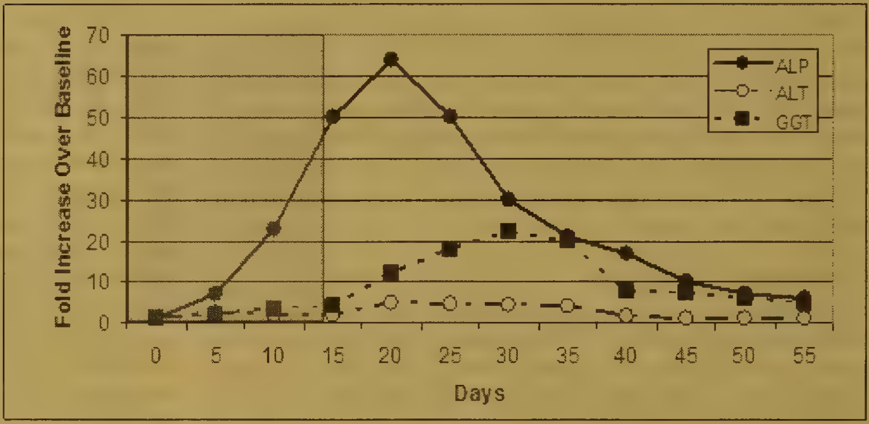
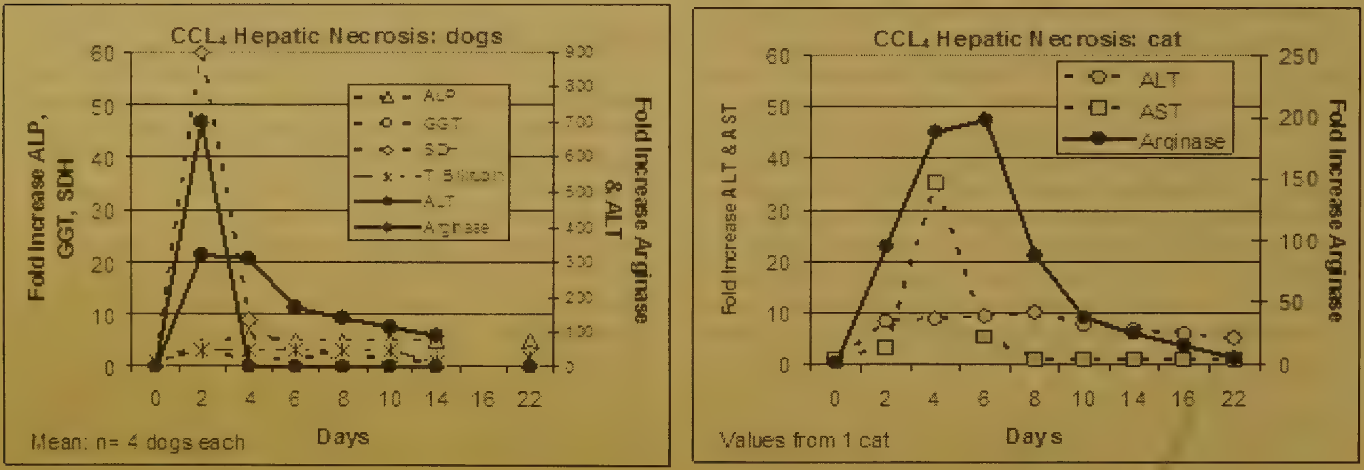


Figure 3. Carbon tetrachloride acute poisoning (necrosis) in dogs *(left)* and cats *(right)*.



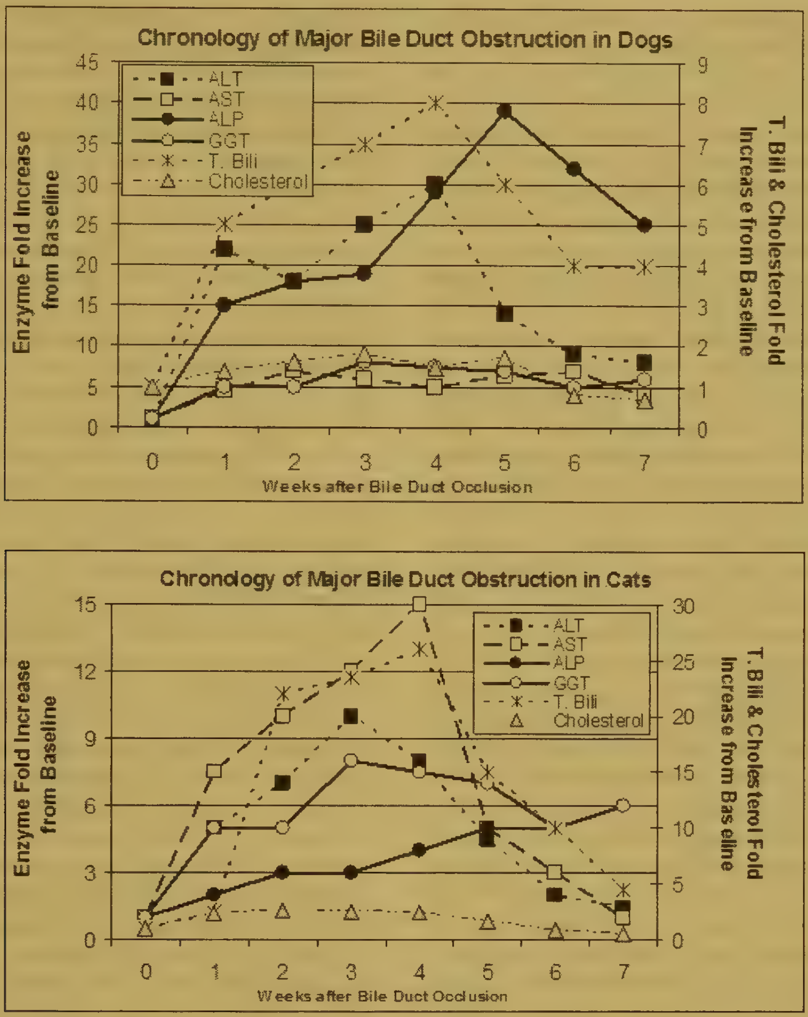


Figure 4. Chronology of major bile duct obstruction in dogs *(top)* and cats *(bottom).*

hepatic veins is another source of shunting proven in cirrhosis where the compromised sinusoidal space promotes "streaming" of blood directly into hepatic venules. These changes restrict hepatocyte access to solutes and contribute to the perception of liver failure irrespective of the metabolic capacity of hepatocytes. Thus, xenobiotic substrate metabolism to estimate "hepatic metabolic function" may simply reflect restricted access to functional tissue.

ORGANIC ANION CHOLEPHILS

Organic anion (OA) cholephil uptake and excretion sensitively reflects hepatobiliary function and perfusion; the endogenous OA cholephils bilirubin and bile acids are proven markers of hepatic disease, cholestasis, and portal perfusion (portosystemic shunting [PSS], TSBA only). Exogenous OA cholephils such as indocyanine green (ICG) and sulfobromophthalein (BSP) (old liver function tests) have been used to investigate the adequacy of hepatic blood and bile flow. Other OAs are used for diagnostic imaging. Hepatocellular OA elimination requires passage into the space of Disse and rapid carrier mediated uptake across the hepatocyte membrane (competition exits between free and conjugated bilirubin, ICG, and BSP *BUT NOT* bile acids). Hepatocellular proteins (eg, ligandin, Y protein, glutathione [GSH] s-transferase, GSH-peroxidase, ketosteroid-isomerase) transport and store OAs in hepatocyte cytosol. Maximal hepatocellular uptake exceeds biliary excretion for most OA; some OAs (BSP, bilirubin, and bile acids) undergo enterohepatic circulation. A number of biliary secretory mechanisms exist for bile acids and other OAs. Conjugated bilirubin, BSP, ICG, and bile acids appear in bile in mixed micelles or macromolecular aggregates. Impaired biliary excretion promotes OA flux into plasma causing high OA concentrations in systemic blood. Understanding excretory processes involved in TSBA management improves test utility in assessment of liver function (perfusion, cholestasis) including high sensitivity and specificity relative to bilirubin or blood ammonia concentrations in detection of serious liver disorders.

TOTAL BILIRUBIN

Bilirubin concentrations assist in the early diagnosis of some forms of liver disease: eg, acute extrahepatic bile duct occlusion (EHBDO), bile peritonitis, cats with hepatic lipidosis, or cats with nonsymptomatic sclerosing cholangitis. As an OA, bilirubin is subjected to the regulatory processes described above. Bilirubin does not compete with bile acids for transport uptake or enterohepatic circulation. Bilirubin pigment originates from heme (senescent RBCs, ineffective erythropoiesis, other "heme" proteins), is modified in the mononuclear macrophage system to unconjugated bilirubin (lipid soluble), circulated to the liver where uptake is followed by glucuronide conjugation (increases water solubility), and are then eliminated in bile. Conjugated bilirubin and an enteric derivative (urobilinogen) undergo enterohepatic circulation with eventual elimination in either urine or bile. Long suggested to assist with differentiation of extrahepatic cholestasis, intrahepatic cholestasis, and hemolytic jaundice, total bilirubin (TB) fractionation into indirect (unconjugated) and direct (conjugated) bilirubin *does not clarify* diagnoses. Rather, total bilirubin concentrations are more useful than bilirubin fractionation in dogs and cats owing to a dynamic flux between forms of bilirubin and distributional compartments, as well as the longevity of protein-bound-bilirubin moieties. For example, dogs with EHBDO (4-week duration) develop TB values 8- to 10-fold normal whereas cats develop TB values up to 25-fold normal. Dogs with hemolytic anemia, especially those receiving blood transfusions, can develop TB concentrations 20-to 30-fold normal. Similar high TB concentrations are observed in some dogs with acute severe hepatic inflammation/infections (eg, dogs with hepatotrophic acute leptospirosis). Furthermore, TSBA concentrations are more sensitive for the early detection of cholestatic disorders.

A further complicating feature of TB as a marker of liver disease is that sepsis (in the absence of primary hepatic involvement) may induce hyperbilirubinemia. This is especially notable in cats. Based on experimental models, hyperbilirubinemia associated with endotoxemia or sepsis reflects impaired hepatocyte bilirubin uptake or impaired canalicular pumps. TB concentrations in cats with hepatic lipidosis are used by the author to predict recovery; survivors generally have a 50% reduction in TB within 10 days of initial treatment. High TB concentrations in cats are easily predicted by finding bilirubinuria (bilirubin is normally absent in cats) whereas a low renal bilirubin threshold exists in dogs such that bilirubinuria is common. While the absence of urobilinogen in jaundice suggests EHBDO, a number of variables influence urobilinogen detection in urine (eg, positive results if enteric bleeding; false positive if urine exposed to light or stored long term). Finding acholic feces in jaundice suggests EHBDO. However, episodes of acholic feces may develop in cats with sclerosing cholangitis or animals with intermittent cholelith associated major duct occlusion.

TOTAL SERUM BILE ACIDS

TSBAs measured enzymatically are routinely used in clinical practice. Available in most veterinary diagnostic laboratories, this test has been adapted to automated analyzers and now to in house testing equipment. TSBA test has been rigorously evaluated in all forms of liver disease including congenital portosystemic vascular anomalies (PSVA) and microvascular dysplasia (MVD). While bile acids do not directly indicate the presence of hepatic encephalopathy (HE), they sensitively detect causal hepatic dysfunction and/or perfusion abnormalities. TSBA supercedes the utility of ammonia in most practices owing to their stability and convenience. The equivalent sensitivity and superior reliability compared to blood ammonia tests for detecting PSS is widely recognized. Best utility occurs when paired fasting (FSBA) and 2-hour postprandial (PSBA) samples are determined. Either serum or heparinized plasma can be used for TSBA measurements; the latter permits submission of smaller blood volumes and faster sample processing in a diagnostic laboratory.

Problems with the TSBA test involve end-point interference by hemolysis and lipemia, the physiologic complexity of the dynamic enterohepatic "challenge," and the potential for overlooking liver disease when only a random or FSBA sample is submitted. Hemolysis interferes with test end point detection (direct enzymatic test) and lipemia can interfere with analyzer endpoint detection causing both spuriously high and low values. All lipemic samples should be clarified (chylomicrons removed by sample chilling and high-speed centrifugation) before bile acid determinations. Understanding the complexity of the enterohepatic endogenous "challenge" is important for trouble shooting unusual test findings: 1) the occasionally encountered "higher" fasting than postprandial SBA concentrations (20% dogs, 5% cats), 2) the need to feed enough food to stimulate gastric emptying and neurohormonal signals initiating/ facilitating gallbladder contraction, bile flow, and enteric motility, and 3) test vulnerability to enteric malabsorption or too rapid enteric transit (limiting endogenous bile acid absorption). FSBA > PSBA reflect differences in gastric emptying and enteric motility, bile bypassing the gallbladder, as well as the normal interdigestive bellows function of the gallbladder, and coordination of gallbladder/enteric contractions, rather than the presence of high unconjugated bile acids (UConjBA) as has been suggested. UConjBA do increase during the late postprandial interval owing to their enhanced formation, higher rate of passive enteric uptake, and lower hepatic uptake compared to conjugated forms; however, only very small concentrations accumulate in normal dogs or dogs with intestinal bacterial overgrowth (picomole rather than micromolar concentrations). While some clinicians use TSBA for serial patient appraisal, there may be limited merit in this practice. In most necroinflammatory liver disorders, architectural change and disturbed perfusion persist. In PSVA, permanent intrahepatic vascular malformations (MVD) may preclude TSBA normalization after shunt ligation. A quantitative association between absolute TSBA concentrations and the "degree," "severity" or nature of liver disease has never been proven (except the shunting pattern: PSBA markedly higher than FSBA concentrations). Marked differences in TSBA values may occur with testing on consecutive days in chronic liver disease, PSVA, and in dogs with MVD. Generally, there is no quantitative value derived from comparing a one day test of 90 μmol/L against a value of 45 μmol/L or 140 μmol/L on closely spaced consecutive samples. Work in the author's laboratory has substantiated that treatment with ursodeoxycholic (UDCA) can cause a spuriously high TSBA concentration in normal dogs. Withdrawal of UDCA for at least one day is thus recommended before TSBA testing in patients receiving this treatment.

A commonly cited study of TSBA in Maltese dogs suggests that high TSBA common to this breed represent either unusual bile acids, cross reacting substances, or interference by lipemia or hemolysis. Data demonstrate significantly increased TSBA measured by the direct enzyme-linked method as well as by individual bile acid concentrations measured by HPLC. Findings in this study are consistent with a diagnosis of MVD, as commonly found in North American Maltese dogs with high TSBA values (80% of some tested kindreds).

URINE BILE ACIDS/URINE CREATININE (UBA/UCr)

To avoid the shortcomings of fasting or randomly collected TSBA values, determination of bile acids in urine (UBA) has been investigated as an alternative with the UBA normalized against a urine creatinine (UCr) concentration (similar to the urine protein/creatinine or urine cortisol/creatinine ratio). Normally, only small amounts of bile acids are eliminated in urine. However, high TSBA in dogs and cats can lead to urinary excretion of water-soluble conjugates and sulfated forms of bile acids (as also proven in human beings). Published peer reviewed work (dogs: n=126; cats: n=79; liver disease: dogs n=102, cats n=54) confirmed that random UBA/UCr can effectively "screen" for abnormally increased TSBA in each species. That work also demonstrated that UBA/UCr of randomly collected urine samples can miss diagnosis of PSVA, similar to a single fasting or random TSBA value. Considering all TSBA tests and all UBA tests performed in that study, each test missed approximately 8% of PSVA dogs. Subsequent work in PSVA dogs proves high dependability of the UBA/UCr value in urine collected 4 to 8 hours after eating (reflecting the lag time involved with urine formation after the postprandial increase in TSBA). This test has potential to be a useful *screening test* for detection of compromised liver function or perfusion.

BLOOD AMMONIA (NH_3)

A product of amino acid metabolism, NH_3 is cleared primarily by urea synthesis in the hepatic Krebs-Henseleit cycle. Because hepatic encephalopathy (HE) is often *but not always* associated with high blood NH_3 concentrations, use of NH_3 for monitoring these patients remains controversial. High blood NH_3 may develop in patients with liver disease as a consequence of PSS, intrahepatic shunting, or because of reduced hepatic mass. However, high NH_3 also can result secondary to enteric bleeding, high protein intake, blood transfusions, PSS in the absence of liver disease, exercise, muscle crush injury, and urinary obstruction or uroabdomen complicated by urease producing bacteria. In detection of PSS, paired TSBA (fasting, postprandial) have equivalent sensitivity to blood NH_3 assessments made after an ammonia challenge (ammonia tolerance test [ATT] using NH_4Cl). Consequently, TSBA concentrations have appropriately displaced NH_3 because of their broader sensitivity for different forms of liver disease and because bile acids are stable in plasma permitting their routine transport to a laboratory for analyses and later analyses. NH_3 concentrations must be immediately measured after blood collection, blood cells must be separated within 15 minutes, samples transported on ice, and a control sample concurrently evaluated. Storage has an unpredictable effect on blood NH_3. A further complicating factor is that the rapid extracorporeal increase of plasma NH_3 in liver patients also has been attributed to high GGT activity (releasing ammonia from peptides) and high circulating glutamine. Enzymatic assays used in most large diagnostic laboratories and in-house dry chemistry methods have undesirable interassay reproducibility. A dry reagent microdiffusion method (dip stick method) based on liberation of gaseous NH_3 in alkaline solution has been touted to be equivalent to a "validated" enzymatic method. The method uses a small amount of whole blood (20 μL) on an alkaline borate buffer-impregnated reagent strip. Liberated NH_3 (gas) diffuses through the pores of a spacer (in reagent strip) reaching a bromcresol-green dye. Color change after 3 minutes is determined using a point of care instrument used to report blood NH_3 concentration (test is linear to 286 μM). Recent experience one unit: erroneous hyperammonemia in 3/25 dogs (12%) screened for PSS (two dogs: paired TSBA < 8 μmol/L, one dog: MVD TSBA = 38 μmol/L; normal TSBA < 25 μmol/L). The ATT can be problematic, difficult to conduct, ([2 mLkg using a 5% solution of ammonium chloride deep in the rectum, blood sampled at 20 and 40 minutes], or oral challenge with NH_4Cl [100 mg/kg, either in solution: dissolved in 20–50 mLwarm water or gelatin capsules, maximal dose 3 g] blood sampled at 30 and 60 min) and may produce signs of HE in PSVA. Furthermore, NH_3 has low sensitivity for detection of hepatobiliary disorders not associated with PSS or HE. Lastly, it is easy to survey for high blood NH_3 concentrations in dogs with PSVA by looking for ammonium biurate crystalluria: check 3 samples 4 to 8 hours after a meal.

PROTEIN C

A noninvasive blood test that assists in differentiating PSVA from MVD, Protein C (PC), a critical short-lived anticoagulant protein, also modulates inflammation and apoptosis. Synthesized in the liver, PC circulates in an inactive form that is activated by interaction with endothelial cells, thrombomodulin and a PC endothelial receptor. Thereafter, PC inhibits activity of several coagulation factors, conversion of prothrombin to thrombin, and production and activity of plasmin (promoting fibrinolysis). PC serves as a prognostic marker in humans and dogs with sepsis (consumption in DIC; involvement with inflammation). Because low PC develops in humans with PSS and hepatic atrophy associated with portal thromboembolism, we hypothesized that it also would reflect PSS in dogs with PSVA or acquired PSS. We confirmed this relationship. A significant reduction in PC activity develops in dogs with severe liver dysfunction as well as PSVA; PC helps differentiate dogs with MVD from PSVA (few dogs with MVD have low PC activity; most PSVA dogs have low PC activity). Low PC activity also documents improved perfusion after PSVA ligation, and functions as a biomarker of dog exposure to food-borne aflatoxin (toxin apparently inhibited protein transcription or secretion).

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HIGH ALP — NOW WHAT?!

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WHAT IS ALP?

Alkaline phosphatase (abbreviated ALP or SAP for serum alkaline phosphatase) is an enzyme present in many species across the animal kingdom. It is a nonspecific metalloenzyme which hydrolyzes many types of phosphate esters at an alkaline pH, in the presence of zinc and magnesium ions. ALP is anchored to the cell membrane by specific proteins called GPI (glycophosphatidylinostol) proteins. When these GPI proteins are broken by bile acids, phospholipase D, or proteases at higher rate, then ALP concentrations in the serum increase above normal.

ALP is present in multiple molecular forms, known as *isoenzymes*. Isoenzymes differ in their sites of action and breakdown, and in their primary functions. Each isoenzyme also has a unique amino acid sequence, immunogenicity, and electrophoretic mobility, making it possible to differentiate the isoenzymes in a diagnostic setting.

ALP ISOENZYMES

Several isoenzymes exist for ALP in dogs and cats. Although some have limited diagnostic utility, they will be reviewed here briefly.

Liver Isoenzyme. This isoenzyme is associated with the hepatocytes and epithelium of the biliary tract. It is an induced enzyme, synthesized in greater quantities during periods of cholestasis. In dogs, the half-life of this isoenzyme is 66 hours, and in cats, the half-life is 6 hours. The clinical significance of the difference in half-lives between species is that any increase in ALP in cats is significant, while a 2- to 3-fold increase in ALP should be considered significant in a dog.

Bone Isoenzyme. Osteoblasts produce this ALP isoenzyme, and it increases with osteoblastic activity. Young animals typically will have an increased ALP activity because of the bone isoenzyme. Some lytic or proliferative bone disorders may also increase ALP. Benign familial hyperphosphatasemia, a genetic condition occurring in some young Siberian Huskies, can increase ALP via increases in this isoenzyme.

Intestinal, Renal, and Placental Isoenzymes. These tissues are sources of small, and usually clinically insignificant, amounts of ALP. In dogs, the half-life of these isoenzymes is less than 6 minutes, and in cats, less than 2 minutes, explaining why they seldom contribute to serum ALP.

Corticosteroid Isoenzyme. In dogs (but not other animals), endogenous or exogenous corticosteroids will cause the hepatic induction of a corticosteroid-associated ALP isoenzyme from the bile canaliculi. Two theories exist as to the formation of the corticosteroid isoenzyme. One theory is that there is up-regulation of a gene in the hepatocyte when it is exposed to corticosteroids, leading to the synthesis of the isoenzyme. The second theory holds that corticosteroids modify the intestinal isoenzyme of ALP, which then is transported to the liver via the portal system for further processing. It takes over a week for this isoenzyme to increase after exposure to corticosteroids; any ALP increase prior to that is likely the result of the liver isoenzyme. The half-life of this enzyme is 70 hours.

CAUSES OF HIGH ALP

Elevations in ALP can be secondary to increased activity of liver, bone, or corticosteroid isoenzymes. They can be grouped into several categories, based on the mechanism of action.

Age Effect. ALP activity may be up to 10 times higher in young, growing animals, owing to the effect of bone isoenzyme. These values decrease by 3 months of age, and are within adult reference values by 15 months of age. As mentioned previously, young Siberian Huskies may have a transient ALP elevation that is markedly elevated for many months beyond that seen in puppies of other breeds.

Breed Effect. Scottish Terriers have been shown to have higher ALP activity than dogs of other breeds. Although this breed has a 2.4-fold incidence of diseases associated with a higher ALP activity (such as hyperadrenocorticism), even Scotties without such diseases had ALP activities higher than other breeds.

Drug Effects. Several drugs commonly used in dogs will increase ALP activity.

- **Glucocorticoids.** In dogs, increased ALP activity is secondary to induction of the corticosteroid isoenzyme. The increase can be marked, up to 100 times normal. Depending on the type of steroid used, the ALP may remain elevated for several weeks.
- **Anticonvulsants.** Phenobarbital, primidone, and phenytoin may also increase ALP activity. The liver isoenzyme is the cause of the elevation.

Hepatobiliary Diseases. Many liver diseases cause elevations in ALP liver isoenzyme, often concurrent with some degree of change in other hepatic biochemical parameters. In cats, the increase in ALP is often of less magnitude than in dogs, owing to the reduced half-life; therefore, any increase in ALP in cats is significant.

- **Extrahepatic cholestasis (bile duct obstruction).** This can cause very high elevations in ALP activity. Pancreatitis may cause elevations in ALP activity through swelling and obstruction of the extrahepatic bile duct.
- **Intrahepatic cholestasis.** Hepatic diseases that primarily affect the periportal (vs. centrilobular) areas will cause a more dramatic rise in ALP activity, primarily because they result in impaired bile flow. Examples of diseases in this category include:
    - **Neoplasia,** In any type of primary or metastatic hepatic neoplasia, rises in ALP activity can be noted, secondary to either the liver and/or

corticosteroid-induced isoenzyme. The ALP rise is secondary to localized cholestasis. In some cases, ALP will be the only liver enzyme abnormality seen on a biochemical panel.

- **Acute hepatocellular injury.** Some cholestasis can be expected secondary to hepatocellular swelling when hepatocytes are injured by trauma, hypoxia, toxins, or other means. However, the rise in AL activity is usually mild and often far less in magnitude than the hepatocellular enzymes ALT and AST.
- **Hepatic lipidosis.** In cats, primary or secondary hepatic lipidosis causes dramatic intrahepatic cholestasis and concomitant elevation in ALP activity, often without a concurrent rise in GGT activity.
- **Periportal inflammation and fibrosis.** Diseases such as cholangiohepatitis in cats and chronic active hepatitis in dogs can lead to elevations in ALP and GGT activity.
- **Nodular hyperplasia.** This benign condition seen in many older dogs leads to disruption of bile flow and induction of an increased ALP activity.

Increased endogenous glucocorticoids. Exposure to chronically elevated levels of glucocorticoids will cause induction of the corticosteroid isoenzyme of ALP and elevation of total ALP activity. This may occur secondary to several sitations.

- **Hyperadrenocorticism.** ALP activity may increase up to 100-fold secondary to this disease. Scottish terriers with hyperadrenocorticism have higher elevations in ALP activity than other breeds with the condition.
- **Vacuolar hepatopathy.** While this pathologic diagnosis can be found with dogs with hyperadrenocorticism or exogenous corticosteroid administration, it can also be secondary to other liver diseases such as reactive hepatopathy, toxin exposure, nodular hyperplasia, and primary inflammatory liver disease. In many cases, vacuolar hepatopathy is idiopathic, and seen in asymptomatic dogs with increased ALP activity. Increases in adrenal sex hormones may be responsible for the vacuolar hepatopathy.
- **Stress-induced.** Endogenous corticosteroids released during times of stress or chronic illness can raise ALP activity 2- to 3-fold.

Increased osteoblastic activity. On some occasions, the bone isoenzyme of ALP will cause a significant increase in ALP activity. Several diseases may lead to this situation.

- **Primary and secondary hyperparathyroidism.** The shifts in bone calcium and phosphorus lead to an increase in ALP up to 3 times normal.
- **Osseous neoplasia.** Primary and metastatic bone tumors may cause a variable increase in ALP activity.
- **Feline hyperthyroidism.** The increase in ALP seen in cats with hyperthyroidism is primarily caused by the bone isoenzyme, with a lesser contribution by the liver isoenzyme.

WORKING UP THE PATIENT WITH HIGH ALP

Presumably, some blood work has been done to discover that the dog or cat has an elevated ALP activity! From there, we will work first backwards, then forwards, to find out the answers we need to know.

Signalment. Here is where we first assess the age of the pet to see if the ALP increase could be because of young age. Remember that most labs list normals for adults, so values may be tagged as abnormal. Breed may also be important. Scottish terriers have higher ALP values even in health, although they also have more diseases associated with high ALP activity. Young Siberian Huskies may also have a high ALP activity of little clinical significance.

History. In adult dogs, the focus of the history is aimed at identifying clues pertaining to glucocorticoids or liver disease. First, a thorough drug history is essential, particularly understanding whether any oral, injectable, ophthalmic, or dermal corticosteroids have been administered in the past few months. Anticonvulsant medications should also be assessed. Next, the owner should be asked about the pet's signs. Polyuria/polydipsia, polyphagia, and weight gain suggest hyperadrenocorticism. Weight loss, anorexia, and vomiting might suggest liver disease.

Physical examination. The exam can also give clues differentiating causes of high ALP. Cushingoid appearance—pot belly, thin haircoat with thin skin and alopecia—may suggest glucocorticoid excess. Ascites, evidence of muscle wasting, and icterus suggest cholestatic liver disease.

Screening laboratory evaluation. Looking at other parameters in the screening blood work can be useful. If other liver enzymes are higher or as high as the ALP elevation, then a primary liver disease should be suspected. If ALP is the only elevation, then a glucocorticoid excess should be considered.

Liver function testing. If there is sufficient concern that the ALP activity increase may be caused by liver disease, then evaluation of fasting and postprandial bile acids may be indicated. Bile acids are a sensitive indicator of liver function, and help identify patients with moderate cholestatic liver disease that has not yet caused hyperbilirubinemia (at which point bile acid testing is unnecessary).

Endocrine testing. Dogs with elevations in ALP that have no history of exogenous glucocorticoid administration should be tested for hyperadrenocorticism. Either an ACTH stimulation test or low-dose dexamethasone suppression test (LDDST) can be used, although the LDDST has higher sensitivity in diagnosing hyperadrenocorticism (95% vs. 75% for the ACTH stimulation test). In cats, evaluation of a total T4 (or a free T4 if needed) can be helpful in cats with an elevated ALP that do not have liver disease.

Abdominal ultrasound. Evaluation of the abdomen via ultrasonography can be very helpful in working up dogs with elevated ALP activity. The liver can be scanned for evidence of biliary obstruction, neoplasia, or other disease, and the adrenal glands can be measured for bilateral enlargement or unilateral masses. If needed, ultrasound-guided aspirates or biopsies can be used to obtain cytologic or histopathologic information about the liver that might contribute to the diagnosis.

HOW FAR DO YOU GO TO GET A DIAGNOSIS?

One of the most frustrating cases is the older adult dog with an isolated ALP activity well above normal (maybe a 4- to 6-fold increase). The dog has no clinical signs—usually the abnormality is picked up on routine annual or pre-dental blood screening. How far do you go to make a diagnosis?

Certainly in my practice I am referred many dogs with just this problem. First, I interrogate the owners about any corticosteroid administration, paying special attention to skin, eye, and ear medications. Then, I evaluate the remainder of the routine bloodwork for any clues regarding the cause of the ALP elevation.

The next step is ruling out hyperadrenocorticism by performing a low-dose dexamethasone suppression test. I will also perform a fasting and postprandial bile acids test to rule out liver dysfunction. The same day, I will perform an abdominal ultrasound to assess the liver and adrenal glands.

If all these tests are normal or negative, then I discuss with the owner what possibilities remain. The primary differentials still left are idiopathic hepatic vacuolar hepatopathy and hepatic nodular hyperplasia. Both of these conditions are benign. I do not advocate hepatic biopsy at that time. Instead, I advise the owner to monitor for signs of any illness, and have the dog's blood work evaluated every 6 months. If clinical signs begin to occur or if other laboratory changes occur, then some testing should be repeated (such as the LDDST) or a liver biopsy should be considered at that time.

HEPATOTOXICITY — THE SILENT STALKER

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> *Quod ali cibus est aliis fuat acre venenum (What is food to one may be fierce poison to others)*
> *—Lucretius, c.99 BCE—c. 55 BCE*

The liver is the metabolic powerhouse of the body. It receives the blood returning from the gastrointestinal tract for processing of incoming amino acids, sugars, and other nutrients, and must also metabolize and detoxify any substances ingested and absorbed through the gastrointestinal tract that might be harmful. We will discuss how the liver is uniquely available as a target for toxicity, the mechanisms of toxicity, the common types and causes of hepatotoxicity in dogs and cats, and the treatment of hepatotoxicity in small animals.

THE LIVER AS A TARGET

The liver is a target for toxins because of its proximity to ingested toxins, its oxygen-poor environment, and its metabolic transformational abilities. It stands as a "security guard" for the body, filtering blood coming from the gastrointestinal tract and dealing with any incoming threats.

Proximity to Ingested Toxins

All of the venous blood from the gastrointestinal tract drains into the portal circulation, which goes directly to the liver. Once the portal blood reaches the liver, it trickles into the sinusoids, contacting the hepatocytes. Therefore, any ingested toxin is going to be taken directly to the liver via the portal circulation.

Oxygen-Poor Environment

The liver receives about 75% of its blood supply from the deoxygenated portal vein, and 25% from the hepatic artery. On the microscopic level, the hepatic acinus is centered around branches of the portal vein and hepatic artery. These drain through the sinusoids toward the central vein. As this occurs, more oxygen is depleted. The area nearest the hepatic artery and portal vein (Zone 1) is least likely to be affected by some toxins, and the area nearest the central vein (Zone 3) is the most likely to be affected by some toxins, since it receives the least oxygen and thus is vulnerable to damage.

Metabolic Transformation

Within the sinusoids, hepatocytes may take up compounds and alter them by various metabolic processes. This may detoxify a toxic compound, make a toxic compound more or less toxic, or make a nontoxic compound toxic. Species and individual variations exist in metabolism. For example, acetaminophen is far more toxic in cats than in dogs because of a relative deficiency of glucuronyl transferase in the liver of cats. Idiosyncratic reactions in individual animals are thought to be caused by differences in metabolic enzymes.

MECHANISMS OF HEPATOTOXICITY

There are several mechanisms at work either alone or concurrently with any toxic event in the liver. The effects on hepatocytes lead to liver damage and illness.

Structural Alteration of Membranes

Some toxins or their metabolites may have a direct effect on cellular or intracellular membranes. They may cause direct damage or an alteration in their chemical or electrical properties, such that their permeability is altered. Carbon tetrachloride, a well-studied hepatotoxin, causes toxicity through several mechanisms, including direct membrane injury.

Inhibition of Membrane Enzymes

Toxins may inhibit enzymes on or within the cellular membrane of hepatocytes, preventing normal function of the cell.

Impairment of Hepatic Uptake Processes

If toxins alter hepatic uptake processes, then nutrients necessary for hepatocyte survival cannot be taken in.

Altered Cytoskeletal Function

The cytoskeleton of a hepatocyte provides its external structure and assists with intracellular transport of bile. Some toxins may damage the integrity of the cytoskeleton, allowing the cell to collapse or intracellular bile transport to be impaired.

Precipitation of Insoluble Complexes in Bile

Bile flow can be impaired if large complexes of insoluble material plug up the bile canaliculi within the liver, creating cholestasis. Some toxins are excreted in the bile as large, insoluble complexes that lead to this problem.

Alterations in Intracellular Calcium

Some toxins will create or allow changes in calcium within the hepatocyte, which can bring metabolic functions of the cell to a halt and cause cell death.

Metabolic Conversion to Reactive Intermediates

Many toxins are metabolized through the P-450 cytochrome oxidase pathway to reactive intermediates, generating free radicals in the process. These free radicals in turn cause further damage.

ACUTE VERSUS CHRONIC HEPATOTOXICITY

Liver toxicity can present in two different clinical syndromes- acute liver necrosis or chronic hepatitis. The difference is caused by the type of toxin, the dose, and the duration of exposure. We will discuss what happens in each type of toxicity.

Acute Hepatotoxicity

In acute hepatotoxicity, the dog or cat ingests a drug or toxin that goes to the liver and causes an acute, fulminant hepatic necrosis. When at least 70% of hepatocytes lose function, then the patient is classified as suffering from acute liver failure (ALF).

As the toxin enters the hepatocytes and alters the cell either directly or through its metabolites, the cell is damaged beyond repair and cell death occurs. Depending on the toxin and the dose, signs of toxicity will be noted from hours to weeks later. For example, cats that develop hepatic necrosis secondary to diazepam usually develop clinical signs 5 to 11 days after oral administration of the drug, while dogs that develop hepatic necrosis secondary to potentiated sulfonamides may take over a month to develop clinical signs.

The clinical signs of acute hepatotoxicity are related to the rapid die-off of hepatocytes. Anorexia, vomiting, and weakness are common, and some patients also exhibit icterus and ascites. Clinicopathologic findings reflect hepatocellular necrosis, with often massive changes in the magnitude of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) activity, with less dramatic changes in alkaline phosphatase (ALP) and gamma-glutamyltransferase (GGT) activity and total bilirubin concentration. Unless liver function is severely depleted, albumin and glucose concentrations remain normal.

Chronic Hepatitis

When the liver is exposed to certain drugs or toxins over an extended period of time, a more chronic reaction can occur, culminating in chronic hepatitis. The pathologic change first seen is an infiltration of the portal area with lymphocytes and plasma cells. The inflammation then spreads to other areas of the liver acinus. This is followed by necrosis, fibrosis, and duplication of bile ductules. The end stage of this process is liver cirrhosis.

The clinical signs of chronic hepatitis are often more subtle than those of acute hepatotoxicity. Weight loss, decreased appetite, icterus, and vomiting may be seen. Clinicopathologically, tests indicative of cholestasis (ALP and bilirubin) are often as high as tests indicative of hepatocellular necrosis (ALT and AST). As the disease progresses and liver function worsens, bile acids concentrations will increase, and eventually serum albumin will decrease.

CAUSES OF HEPATOTOXICITY

Almost any drug can cause an idiosyncratic reaction of hepatotoxicity in any individual. However, several drugs are well known for having a propensity for causing liver damage in a larger than expected population. Many toxins also have a primary effect on the liver. Many of the more common drugs and toxins causing hepatotoxicity in dogs and cats are listed in Table 1.

TREATMENT OF HEPATOTOXICITY

Treatment of hepatotoxicity is aimed at both supportive care and specific treatment for the toxin, if one is available. Specific treatments should be instituted as soon as possible. For example, dogs with acetaminophen toxicity should be treated with n-acetylcysteine, ascorbic acid, and cimetidine, as well as supportive care for liver toxicity.

Fluid and Electrolyte Therapy

Supportive care for acute hepatotoxicity starts with fluid therapy. Correction of fluid and electrolyte imbalances is essential in providing he environment for healing to take place. Occasionally, colloids such as hetastarch may be needed to help in patients with decreased colloid oncotic pressure, such as those with hypoalbuminemia.

Therapy of Hepatoencephalopathy

Patients with hepatotoxicity should be monitored for clinical evidence of hepatoencephalopathy (HE). Signs of HE secondary to hepatotoxicity usually include a rapid onset of behavior change, ataxia and stupor, followed by seizures. Blood ammonia concentrations can be evaluated to confirm a diagnosis of HE. Treatment of

Table 1. Common Causes of Hepatotoxicity in Dogs (D) and Cats (C)

Therapeutic Drugs	Toxins
Phenobarbitol (D)	Zinc (D)
Primidone (D)	Iron (D)
Phenytoin (D)	Aflatoxins (D)
Diazepam (C)	*Amanita* sp. Mushrooms (D)
Stanozolol (C)	Microcystins from blue-green algae (D)
Diethylcarbamazine-oxibendazole (D)	Pennyroyal oil (D, C)
Trimethoprim-sulfadiazine (D)	Pine oil (C)
Carprofen (D)	Lily of the Valley (D)
Ketoconazole (D)	Carbon tetrachloride (D, C)
Acetominophen (D)	

HE is aimed at reducing blood ammonia concentration. Lactulose, a nonabsorbable disaccharide, is given orally or rectally. Lactulose is metabolized in the colon by bacteria, creating a more acidic environment which traps ammonia in the colon and doesn't allow it to be absorbed into the body. Neomycin can also be given to decrease the gut bacteria which produce the ammonia.

Treatment of Coagulopathy

Coagulopathy can occur in severely affected patients with acute hepatopathy or chronic hepatitis. The liver synthesizes almost all of the coagulation proteins, so when liver failure occurs secondary to hepatotoxicity, there is a strong risk of coagulopathy. This can be treated with transfusions of fresh frozen plasma or fresh whole blood, which contain adequate amounts of coagulation factors. Ultimately, however, the liver must regenerate enough function to regain clotting factor production for long-term health.

Anti-inflammatory Treatment

With chronic hepatitis, the chronic inflammatory reaction may dissipate once the drug or toxin has been removed. However, in some cases, anti-inflammatory treatment with prednisone or prednisolone is used to treat patients with chronic hepatitis initiated by a drug or toxin. Ursodiol, a synthetic analog of a hydrophilic bile acid, is thought to act as an anti-inflammatory in some cases of chronic hepatitis in humans, and it is often prescribed for this in small animals as well, although there are no controlled studies proving its effectiveness.

Antioxidant Therapy

Many hepatotoxins damage the liver by creating oxygen-derived free radicals. Antioxidants may help negate the effects of these free radicals and minimize the liver injury. Vitamins C and E are often given for their antioxidant qualities, and the herbal supplement milk thistle (or its extract silymarin) can be used in pets with both acute and chronic hepatotoxicities. The supplement s-adenosyl-L-methionine (SAMe) is a donor of glutathione, which can bind to (and disarm) oxygen-derived free radicals. Unfortunately, no controlled studies exist on the clinical benefit of either silymarin or SAMe in liver disease. Although anecdotal reports are favorable, hopefully a blinded, controlled study of these therapies will be performed in the near future.

DIAGNOSIS OF HEPATIC DISEASE

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Clinical signs of gastrointestinal disease, such as vomiting and diarrhea are extremely common in small animal patients. When seeking advice from a veterinarian pet owners expect accurate diagnosis and definitive therapy of the problem. In very few cases the diagnosis can be made by history and physical examination alone and the veterinarian has to utilize diagnostic tests to arrive at the diagnosis. The challenge for the veterinarian is to choose the most appropriate diagnostic test to arrive at the most accurate diagnosis.

In general, the clinician is guided by the golden rule to only perform a diagnostic test when the outcome of the test will have an impact on the management of the patient. This golden rule can be expressed more scientifically by stating that a diagnostic test should only be performed if the post-test probability for a disease is either significantly smaller or significantly larger than the pre-test probability.

Other, more commonly used parameters to assess the clinical usefulness of diagnostic tests are sensitivity, specificity, accuracy, positive predictive value, and negative predictive value. **Sensitivity** is the number of true positive patients divided by the number of all patients with the disease and is thus a measure of how well a diagnostic test identifies patients with a disease. **Specificity** is the number of true negative test results divided by the total number of patients without the disease and is thus a measure of how well the test distinguishes patients with the disease from those that do not have the disease. **Accuracy** is the sensitivity multiplied with the specificity and gives the clinician a sense of the overall performance of the test. Sensitivity and specificity are characteristic for each test and are not influenced by the prevalence of the disease. However, for clinical practice the clinician also needs some sense of how to interpret a test result in light of the population tested. **Positive predictive value** is the number of true positive test results divided by the total number of positive test results and is thus a measure for the confidence the clinician can place into a positive test result. The **negative predictive value** is the number of true negative test results divided by the total number of negative test results and is thus a measure of how confident the clinician can be to exclude the disease in a patient with a negative test result. Whenever possible the prevalence of the disease in the test population should be taken into consideration when evaluating the clinical usefulness of a new diagnostic test.

While some diagnostic tests are either negative or positive, most diagnostic tests will yield a quantitative result that needs to be interpreted. This is achieved by comparison of the result found in a diseased animal to that found in a healthy animal (reference, control, or normal range). However, a result outside the reference range does not necessarily indicate disease and cut-off values need to be determined that afford the best test characteristics for the diagnosis of a disease. A result outside the reference range may have different implications for different tests. For example if the upper limit of the reference range for serum creatinine concentration is 1.5 mg/dL a result of 1.8 mg/dL may very well be significant, while a serum ALT activity of 76 U/L in a dog may be of no significance when the reference range is 0 to 65 U/L. Therefore, a cut-off value for each diagnostic test must be identified, that determines whether an abnormality is significant enough to warrant diagnosis of a disease.

SERUM CHEMISTRY PROFILE

Serum activities of hepatic enzymes are analyzed as markers for hepatobiliary disease in both dogs and cats. Unfortunately, some of these enzymes are also synthesized in other tissues. Therefore, elevations of serum activities of hepatic enzymes outside the control range can be seen with many non-hepatic conditions.

Alanine aminotransferase (ALT) is a cytosolic enzyme of hepatocytes and leaks into the vascular space during hepatocellular damage. The serum half-life for ALT is rather short (1–2 days). Mild elevations of serum ALT activities are considered nonspecific for hepatocellular injury but moderate to severe elevations are cause for concern and should prompt immediate further work-up of the patient for possible hepatobiliary disease.

Alkaline phosphatase (ALP) shows species-specific differences. In the dog elevated serum ALP activities are most commonly due to hyperadrenocorticism, iatrogenic drug therapy (glucocorticoids, phenobarbital, or other), or biliary disease. However, primary hepatic disease can also be associated with elevations of serum ALP activities. In cats, serum ALP activities are more specific for hepatobiliary disease.

Gamma glutamyl transferase (GGT) is also nonspecific for liver disease in dogs and cats but is more sensitive for liver disease in cats than it is in dogs.

Serum blood urea nitrogen, serum cholesterol, and serum albumin concentrations can all be decreased in dogs and cats with hepatic failure. However, these findings are rather insensitive and are also not specific for hepatic failure.

SERUM OR PLASMA AMMONIA CONCENTRATION

Plasma ammonia concentration can be used as a crude indicator for the presence of hepatic encephalopathy. Serum or plasma needs to be placed on ice immediately after collection and needs to be analyzed rapidly. However, a plasma ammonia concentration in the reference range does not exclude hepatic encephalopathy as many other substances have been implicated in the pathogenesis of this condition.

Some clinicians have recommended the use of an ammonia tolerance test. However, the author does not believe that an ammonia tolerance test yields any further information compared with pre- and postprandial serum bile acid concentrations.

A recent study has suggested that the measurement of plasma ammonia concentration is superior to serum bile acids concentrations for the diagnosis of portosystemic shunts in dogs.

SERUM BILE ACID CONCENTRATIONS

Bile acids are metabolites of cholesterol degradation. They are formed and conjugated in the liver and secreted in the bile. After a meal cholecystokinin stimulates gall bladder contraction and release of bile into the duodenum. Conjugated bile acids play a crucial role in fat absorption as they help to emulsify fat. A small amount of bile acids are deconjugated by the small intestinal microflora. These unconjugated bile acids are absorbed in the small intestine and are no longer available for fat emulsification. In contrast, conjugated bile acids are absorbed in the ileum, reach the vascular space, and are extracted from the portal blood by the liver.

Pre- and postprandial serum bile acid concentrations are used for the diagnosis of hepatic impairment and portosystemic shunting. Food is withheld from the patient for 12 hours and a serum sample is collected. A small amount of food, rich in fat, is fed to stimulate gall bladder contraction and another serum sample is collected 2 hours later.

When hepatic function is significantly impaired extraction of bile acids from the portal blood becomes less efficient and both pre- and postprandial serum bile acid concentrations increase. In patients with portosystemic vascular anomalies pre-prandial bile acid concentrations maybe only slightly increased, while post-prandial serum bile acid concentrations are often severely increased. However, the pattern of serum bile acid concentrations is not diagnostic of a specific hepatobiliary disorder and can only suggest the likelihood of one over another disorder.

In some normal patients, paradoxical results are observed in that pre-prandial bile acid concentrations are higher than post-prandial concentrations. It has been speculated that this finding is due to gall bladder contraction without food intake. However, it is important to note that this interpretation requires that both pre- and post-prandial serum bile acid concentrations are below the upper limit of the reference range for post-prandial serum bile acid concentrations. Also, increased pre-prandial bile acid concentrations have been found in dogs with evidence of an altered small intestinal microflora.

Recently, the use of sulfated and non-sulfated urinary bile acid concentrations in dogs and cats with suspected hepatic disease has been described. However, further studies are necessary before their routine use can be suggested instead of serum bile acid concentrations.

^{13}C-AMINOPYRINE DEMETHYLATION BLOOD TEST

The aminopyrine breath test (ABT) has been shown to be useful in quantifying hepatic microsomal enzyme function in human beings and laboratory animals. Aminopyrine, a compound chemically similar to the non-steroidal anti-inflammatory drugs antipyrine and phenylbutazone, is demethylated by microsomal enzymes in the liver. The liberated methyl groups are oxidized to CO_2, which diffuses into the blood stream, reaches the pulmonary alveoli, and is released into the expiratory air. The administration of aminopyrine labeled with either ^{13}C or ^{14}C isotopes allows for the specific measurement of CO_2 derived from aminopyrine, by detection of CO_2 isotopes released in the expiratory air.

Reproducible collection of breath samples can be difficult in veterinary species. Therefore, a ^{13}C-aminopyrine demethylation blood test has been developed and is currently being evaluated in dogs and cats that undergo hepatic biopsy. Initial results have been promising.

CYTOLOGY

Cytology can be useful in arriving at a specific diagnosis in patients with a hepatopathy. However, cytology does not allow evaluation of hepatic architecture. Thus, the number of conditions where hepatic cytology is clinically useful is limited to hepatic neoplasia (if cells exfoliate) and hepatic lipidosis.

LIVER BIOPSY

A liver biopsy is the best diagnostic test to arrive at a definitive diagnosis in pets with liver disease. A biopsy can be collected by use of an ultrasound-guided Tru-cut biopsy, by laparotomy, or by laparoscopy. The advantage of laparoscopy and laparotomy are that bigger pieces can be collected under direct visualization and that complications, such as bleeding, can be identified more rapidly. However, laparoscopy and laparotomy are also more invasive than a Tru-cut biopsy. No matter what method is chosen, the patient must be carefully evaluated before collection of a hepatic biopsy. This evaluation should include complete blood work, but also a coagulation profile, a platelet count, and a buccal mucosal bleeding time. Multiple biopsies must be taken. One biopsy should be cultured and in dogs a second one should be stored for copper analysis if the histopathologist raises any questions concerning copper accumulation in the liver. After a biopsy is collected the patient should be carefully evaluated to identify any potential bleeding.

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TRITRICHOMONAS FOETUS – SHOULD I WORRY ABOUT IT?

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Over the last decade *Tritrichomonas foetus*, a protozoal organism previously known as a pathogen in the reproductive tract of the bovine, has been recognized as an important pathogen in the gastrointestinal tract of cats. *Tritrichomonas foetus* is a flagellated protozoal parasite. Diarrhea has been reported in cats after both experimental and natural infection with *Tritrichomonas foetus*. Although the true prevalence of *T. foetus* infection in cats is unknown, it is suspected to be relatively high. In one study, 31% of 117 cats examined at an international cat show were found to be infected with *T. foetus*.

While cats of any age, breed, or sex can be infected, young cats that are densely housed (eg, cats in catteries, animal shelters, or multi-cat households) seem to be at increased risk. Infection is most commonly seen in young cats (ie, those that are less than 12 months of age) but older cats may also be infected. *T. foetus* primarily colonizes the surface of the colonic mucosa, leading to chronic large bowel diarrhea. Without appropriate treatment cats usually remain persistently infected. While diarrhea may spontaneously resolve, cats will often experience recurrent bouts of diarrhea after being exposed to stress. Cats infected with *T. foetus* generally appear healthy but show an increased frequency of defecation with loose to liquid stools, which may contain blood and/or mucus. Fecal incontinence is frequently observed. The anal region may appear edematous and may become painful with severe diarrhea. A rectal prolapse may occur in some cases.

DIAGNOSIS

Diagnosis of a *T. foetus* infection can be made by identification of trophozoites on a direct fecal smear examination, fecal culture, polymerase chain reaction (PCR) analysis of fecal material, or by colonic mucosal biopsy. Disadvantages of a direct fecal smear examination include a low sensitivity (14%), low specificity (*T. foetus* can be misdiagnosed as *Giardia* spp. or the nonpathogenic *Pentatrichomonas hominis*), and the fact that only fresh fecal samples can be used.

Tritrichomonas foetus can also be cultured in-house using the commercially available culture system In Pouch™ TF (Biomed Diagnostics, San Jose, CA). Pouches should be inoculated with less than 0.1 g of freshly voided feces and then incubated at 25°C. Pouches need to be evaluated under a microscope every couple of days. Results are usually obtained between 1 and 11 days of setting up a pouch. Although fecal culture is more sensitive than direct fecal smear examination, difficulties in interpretation of results, the necessity of using freshly voided feces, and the fact that results might not be available for up to 11 days, are important disadvantages of this method.

T. foetus DNA can be amplified from fecal samples by PCR. PCR has been shown to be the most sensitive method for detecting *T. foetus* in fecal samples, and is ideally suited for direct diagnosis of *T. foetus* infection. Advantages of PCR testing compared with culture include a higher sensitivity, faster turnaround time, and easier handling and storing of samples since DNA is relatively stable under various temperature conditions.

THERAPY

Until recently, successful treatment for *Tritrichomonas foetus* infections in cats was not available. However, a recent study has shown that administration of ronidazole (30–50 mg/kg PO twice daily for 2 weeks) is effective in both resolving diarrhea and eradicating *T. foetus*. It should be noted that ronidazole is not approved for use in domestic animals so obtaining signed consent from the owner before initiating therapy may be wise. Recently, several compounding pharmacies have started offering ronidazole. Some examples are Diamondback Drugs (phone: 1-866-646-2223; www.diamondbackdrugs.com), Pet Health Pharmacy (phone: 1-800-742-0516; www.pethealth pharmacy.com), Abrams Royal Pharmacy (phone: 1-800-458-0804; www.abramsroyalpharmacy.com), Westlab Pharmacy (phone: 1-800-493-7852; www.westlabpharmacy.com), and Creative Compounding (phone: 1-800-672-2177), but other compounding pharmacies may also carry ronidazole. Some cats have developed similar neurologic signs as have been reported as a side effect of metronidazole therapy. These neurologic signs are most likely reversible if the medication is stopped.

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INTERPRETATION OF ELEVATED LIVER ENZYMES

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Abnormal liver enzymes are frequently found on the biochemical profile. In a study of 1,022 blood samples taken from both healthy and sick dogs and cats 39% had alkaline phosphatase (ALP) increases and 17% had alanine aminotransferase (ALT) increases. Abnormal liver enzymes identified in asymptomatic dogs reflect occult liver changes that require further investigation and should not be ignored. The symptomatic or sick animal with abnormal liver enzymes could have primary liver disease but the changes could easily also be the result of some other primary non-hepatic disease. Careful investigation for drugs, intoxicants, and other diseases that could affect the liver should always be considered. Based on the "clinical picture" obtained of the patient a reasonable diagnostic approach can be formulated. A review of liver enzymes and a protocol for further investigation is discussed in this article.

LABORATORY TESTS

It is important to understand basic liver-related laboratory tests in order to determine the possible etiologies for abnormal levels and to develop a course of action. Many liver tests are not specific only to the liver but can be abnormal from primary non-hepatic disease as well. Evaluation of liver biochemical tests must be interpreted in light of the history, medications and clinical findings. The magnitude and duration of increase is also dependent on the type, severity and duration of the stimulus and the species. They do not prognosticate the irreversibility of liver disease at any one point in time. Also, because the liver is involved in so many functions no single laboratory test in this category reflects the complete functional state of the liver. Liver biochemical test are categorized into groups that reflect 1) hepatocellular injury, 2) cholestasis, or 3) tests of impaired metabolic function or synthetic capacity.

Indicators of Hepatocellular Injury

Canine and feline hepatocyte cytoplasm is rich in ALT and contains lesser amounts of aspartate aminotransferase (AST). Altered permeability of the hepatocellular membrane caused by injury or a metabolic disturbance results in a release of this soluble enzyme. Conceptually ALT and AST should be thought of as hepatocellular "leakage enzymes." Subsequent to an acute, diffuse injury, the magnitude of increase crudely reflects the number of affected hepatocytes. It is, however, neither specific for the cause of liver disease nor predictive of the outcome. The plasma half-life of ALT activity is 12 to 24 hours; however, ALT concentrations may take days to decrease following an acute insult. Persistent increases of ALT are characteristic of chronic hepatitis in the dog.

A variety of tissues, notably skeletal muscle and liver, contain high AST activity. Hepatic AST is located predominantly in hepatocyte mitochondria (80%) but also is soluble in the cytoplasm. Skeletal muscle inflammation invariably causes a serum AST increase (and ALT to a much lesser extent) that exceeds the serum ALT activity and can be further defined as muscle origin by the measurement of the serum creatine kinase activity (CK) a specific muscle enzyme. Clinical experience in veterinary medicine indicates that there is value in the interpretation of the serum activities of ALT and AST for liver disease. Following an acute injury resulting in a moderate to marked increase in the serum ALT and AST concentrations, the serum AST will return to normal more rapidly (hours to days) than the serum ALT (days) due to their difference in plasma half-life and cellular location. By determining these values every few days following an acute insult, a sequential "biochemical picture" indicative of resolution or persistent pathology is obtained.

Markers of Cholestasis and Drug Induction

Alkaline phosphatase (ALP) and gamma-glutamyltransferase (GGT) show minimal activity in normal hepatic tissue but can become markedly increased in the serum subsequent to increased enzyme production stimulated by either impaired bile flow or drug-induction. These enzymes have a membrane bound location at the canalicular surface; ALP associated primarily with the canalicular membrane and GGT associated with epithelial cells comprising the bile ductular system. With cholestasis, surface tension in the canuliculi and bile ductules increases and these surface enzymes are then up-regulated in production. The plasma half-life for hepatic ALP in the dog is 66 hours in contrast to 6 hours for the cat and the magnitude of enzyme increase (presumably a reflection of the synthetic capacity) is greater for the dog than the cat.

Elevations in ALP in the dog can be due to a number of isoenzymes other than hepatic cholestasis. There are only two isoenzymes of ALP that are diagnostically important: bone and liver. Bone source from osteoblasts is elevated in young growing dogs before their epiphyseal plates close and in osteoblastic bone tumors. A recent study identified some dogs with osteogenic bone tumors with increased ALP concentrations to have a poorer prognosis suggesting diffuse bone metastasis.

An increase in the serum ALP (and GGT activity) can be associated with glucocorticoids (endogenous, topical or systemic), anticonvulsant medications, and possibly other drugs or herbs in the dog. There is remarkable individual variation in the magnitude of these increases and with glucocorticoid-induced elevations, there is no concomitant hyperbilirubinemia. A moderate to marked increase in serum ALP activity without evidence of primary liver disease is most compatible with steroid-induction and warrants a review of the patient's history (topical or systemic glucocorticoids) or evaluation of adrenal function. The glucocorticoid-stimulated production of ALP isoenzyme in the dog can be distinguished from the cholestatic-induced hepatic ALP isoenzyme by several procedures. It was initially thought that the glucocorticoid-associated isoenzyme could be used as a marker of exogenously administered corticosteroids or increased production of endogenous glucocorticoids but unfortunately, the glucocorticoid-associated isoenzyme is also associated with hepatobiliary disease as well. It is important to note that steroids will also cause usually mild increases in ALT as well.

Increased serum GGT activity is associated with impaired bile flow in the dog and cat and glucocorticoid administration in the dog. Bone does not contain GGT; therefore, growth and bone disease are not associated with increased serum GGT activity. The administration of anticonvulsant medications to dogs causes mild or no increase in the serum GGT activity. As a marker of hepatobiliary disease, the measurement of serum GGT activity does not appear to provide a diagnostic advantage over the serum ALP determination in the dog; however, it is reported to be a more sensitive marker in cats having biliary tract disease.

Evaluation of Liver Function

On a routine biochemical profile, it is important to note the liver function tests including bilirubin, albumin, glucose, BUN, and cholesterol. Albumin is exclusively made in the liver and if not lost through renal or GI tract, sequestered or diluted, a low concentration would suggest significant hepatic dysfunction. It is said to take greater than 60% loss in hepatic function for albumin concentrations to decline. Major clotting factors are also made in the liver therefore prolonged clotting time suggests significant hepatic dysfunction. Liver disease with concurrent abnormal function tests suggests a guarded prognosis.

The most sensitive function test we have readily available in small animals are serum bile acids. The serum total bile acids (SBA) concentration is a reflection of the efficiency and integrity of the enterohepatic circulation. Pathology of the hepatobiliary system or the portal circulation results in an increased SBA prior to the development of hyperbilirubinemia, negating its usefulness in the icteric patient. An increase is not specific for a particular type of pathologic process but is associated with a variety of hepatic insults and abnormalities of the portal circulation.

The current suggestion for the determination of the SBA is to differentiate between congenital portal vascular anomalies and liver insufficiency prior to the development of jaundice or abnormalities in other function tests. Identifying abnormal SBA would support the decision to obtain further liver diagnostics or histology. When the fasting or postprandial SBA value is greater than 25 µmol/L for the dog and cat, there is a high probability that the histology findings will define a lesion. When using these guidelines it is prudent to recognize that a small number of healthy dogs have been reported with SBA values above 25 µmol/L. We have occasionally observed the measurement of a fasted SBA value greater than the postprandial SBA value. The reason for this non sequitur is unclear but probably multifactorial and is only significant when one or both of the concentrations is abnormal. Recently, urinary bile acids have become available and urinary bile acids provides similar information to what is obtained from serum bile acids and neither test appears to be better than the other. The advantage of urinary bile acid measurements would be for the screening of litters of young puppies for suspected inherited vascular anomalies where urine collection is simpler than paired serum samples.

In summary, there are a variety of markers with variable sensitivity and specificity that reflect hepatic tissue and portal vasculature pathophysiology. We support the conclusion of another study that found that the optimal test combination is the serum ALT activity and bile acid concentrations. This pairing provided the best sensitivity and specificity, respectively for the diagnosis of hepatocellular disease.

DIAGNOSTIC STRATEGIES

In the asymptomatic patient with an increased liver biochemical test(s) the increased value should be confirmed at least once to exclude a spurious result from laboratory error and to avoid unnecessary and costly additional testing. A careful history is essential to exclude drug associated enzyme elevations. The signalment of the patient may also provide an insight to the possible etiology of the enzyme increase. For example old dogs frequently have benign nodular hyperplasia, neoplasia, or systemic disease while younger to middle aged dogs more commonly have chronic hepatitis or portal systemic shunts. There are also certain breeds that are predisposed to develop chronic hepatitis. A careful physical examination may also provide clues to the diagnosis. The most common cause of abnormal liver enzymes is not primary liver disease but rather reactive hepatic changes occurring secondary to other non-hepatic diseases. These would include such conditions as intra-abdominal disorders (inflammatory bowel disease, nutritional abnormalities), cardiovascular disease or metabolic derangements as a few examples. Generally these secondary changes are reversible once the primarily disease is treated. Successful resolution of the non-hepatic disease and continued abnormal liver enzymes would be a strong indication for further investigation of the liver.

If no likely explanation for the laboratory abnormalities can be found there are two courses of action that one can take; either begin a diagnostic evaluation of the patient starting with bile acid determinations, or re-evaluate the patient's liver enzymes at a later date. A rational wait period for re-evaluation is 4 to 6 weeks giving consideration to the half-life of liver enzymes and the time needed for recovery from an acute occult hepatic injury. During the waiting period it is also reasonable to consider a course of antibiotic therapy or perhaps liver support therapy. However, it is best not to delay retesting and further diagnostics beyond the 6 weeks in the event that an active disease process may progress.

Imaging

Routine abdominal radiographs are helpful in determining liver size and shape and for detection of other intra-abdominal disorders. Ultrasonography is noninvasive, readily available and is the most informative initial imaging modality for liver disease. It often complements the clinical and laboratory findings and is useful for identifying focal liver lesions, diffuse liver disease or biliary disease. Frequently, fine needle aspiration (FNA) for cytologic evaluation is performed in conjunction with ultrasound. Although FNA is safe and easy to perform, one must be cautious in the interpretation of the results and use the FNA findings in conjunction with clinical signs and other diagnostics to make a diagnosis. The sensitivity and specificity is not very high when results are compared with histopathology. We find the best correlation of aspirates with hepatic neoplasia and diffuse vacuolar hepatopathies and the poorest in patients with chronic hepatitis.

Liver Biopsy

Although our diagnostic techniques continue to improve, in most instances imaging and biochemical testing cannot replace a liver biopsy. This is by far the best examination for a definitive determination of the nature and extent of hepatic damage and to appropriately direct the course of treatment. The method for liver biopsy procurement may be surgery, needle biopsy, or laparoscopy. Each has certain advantages and disadvantages and the decision of which procedure to use should be made in light of all the other diagnostic information, always considering what is in the best interest of the patient and client.

KEY POINTS OF LIVER DISORDERS

ALT and Young Dogs

ALT elevations in young dogs under 1 year of age are sometimes associated with portal vascular anomalies, and bile acid concentrations should be obtained to exclude that possibility. Occasionally I see young dogs under 1 year of age with unexplained ALT increases and normal bile acids correct over time. If the ALT is abnormal, bile acids are normal, and there are no symptoms I take a wait and see approach.

Reactive Hepatopathies

This category represents the secondary changes that take place from a variety of systemic and metabolic disease. Examples include inflammatory disorders, cardiopulmonary, neoplasia, gastrointestinal nutritional and endocrine disorders. Variable ALT and ALP increases but usually normal liver function tests are the norm. The histology is variable and often includes vacuolar changes (see Vacuolar Hepatopathy below), mild inflammatory changes, and cholestasis.

Chronic Hepatitis

The most important diagnosis of liver disease to make in the dog is chronic hepatitis. Early diagnosis and prompt therapy improves patient survival. Abnormal hepatic copper metabolism appears to be associated in many breeds and copper chelator therapy is successful in most. Hepatitis often begins in dogs at 2 to 5 years of age, beginning with only ALT increases and then later other enzymes and function tests become abnormal. Females are over-represented and certain breed-associated hepatitis is reported. Dogs with significant hepatitis usually also have concurrent bile acid abnormalities.

Vacuolar Hepatopathies

This condition appears to becoming more common or our awareness and advanced diagnostic workup make it seem so. Hepatic vacuolar “steroid-like changes” occur secondary to endogenous and exogenous steroids. A recent study found most dogs having this change but not associated with glucocorticoids had a chronic illness. It is suspected endogenous stress related cortisol release to be the cause. However, some older dogs have an idiopathic vacuolar hepatopathy associated with increased ALP steroid isoenzyme. Investigation for hyperadrenocorticism is negative and concurrent disease has been excluded in these cases. It is postulated that possibly other adrenal steroids (progesterones or estradiols) may also be responsible in some cases. It is known that progesterones bind to the hepatocyte corticosteroid receptors and can induce ALP production. Scottish terriers also have yet unexplained increases in serum ALP and vacuolar changes.

Hepatic Nodular Hyperplasia

A benign condition, hepatic nodular hyperplasia is usually associated with ALP and variable ALT increases. Dogs are asymptomatic and generally older than 10 years of age. Abdominal ultrasound identifies multiple hyper or hypoechoic nodules in the liver and a wedge biopsy is needed for confirmation.

Hepatic Neoplasia

Occasionally I see dogs with hepatic adenomas or carcinomas that have no clinical signs but increased ALP concentrations. Abdominal ultrasound will identify a liver mass. Hepatic adenomas are slow growing but can sometimes become necrotic and bleed. Surgical removal of a liver mass is recommended.

SUMMARY

Abnormal liver enzymes should not be ignored and should be investigated in a systematic manner as previously discussed. In asymptomatic animals with no evidence of significant or treatable disease or in situations where financial constraints limit further workup, the patient should be fed a quality maintenance diet for the patient's stage of life and the possibility of instituting specific liver support therapy should be explored.

A CONTRACTOR'S VIEW: HOW TO BUDGET AND BUILD A VETERINARY HOSPITAL

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OBJECTIVES

Demonstrate how to prepare a complete project budget helping you to understand how much and where your money is going to complete a construction project. Do you have everything accounted for? This article provides an overview of the most common methods of building a veterinary hospital. Which is best for you?

BUDGETING A VETERINARY HOSPITAL

- **Design/builders budget:** Architectural, engineering and construction budgeting (Table 1)
- **Owner's managed budget:** Business systems, land, banking, legal, impact fees, equipment (Table 2)

METHODS OF BUILDING A VETERINARY HOSPITAL

- Design, Bid, Build – Pros and Cons
- Design, Construction Management – Pros and Cons
- Design, Build – Pros and Cons

Design, Bid, Build: - Traditional Method

- You find an architect.
- Develop your project's program (definition) and budget.
- Your architect designs your building based on your program.
- You and the architect review and revise the design until you are satisfied with it.
- Your architect produces construction documents from the design drawings – plans, specifications, bid, and contract forms.
- You define the bidder's list:
  By invitation, open bidding, or negotiate with a pre-selected contractor.
- Bids are received and evaluated by you and your architect who makes a recommendation. Actual cost of the project is now known
- You select the builder and sign a contract for construction.
- During construction your architect, or a separate inspector, reviews progress periodically and reports, and processes contractor payment requests, and change orders.
- The contractor is responsible for building according to the construction documents.

Pros

- Traditional method is understood by contractors, subs, banks, etc.
- High level of design control, Project is program driven

Cons

- Potential adversarial relationship between architect and contractor
- Low level of cost control – Cost are not known until after bidding
- High level of owner's time

Design – Construction Management

- Program and design phases similar to Design-Bid-Build.
- A construction manager (CM) acts on your behalf during the process.
- Several types of construction managers:
  - As owner's agent – usually is involved from the beginning – helps program. Is involved during design and bidding and acts as your inspector during construction. Usually is affordable only on larger projects. ($2 to $3 million+)
  - As contractor – Also takes the place of the general contractor. Solicits bids from subs directly, schedules, and supervises the work. Fee based on hourly rates, lump sum fee or percent of construction cost. Can potentially save general contractors mark-up to offset construction manager's fees.
- Actual cost of project is known after all trades have been bid.

Pros

- CM is owner's agent
- CM can assist in estimating, evaluate cost of design
- CM can introduce cost savings by eliminating general contractor's markup
- High level of cost control
- Owner's involvement time is reduced

Cons

- CM is an additional player with additional expense
- Cost of project is not known until after all bidding is complete
- Potential for adversarial relationship between architect and CM
- Owner's risk for overruns is increased

Design-Build

- Design and construction cost can be balanced in the design phase.
- The designer and builder are the same entity.
- Programming and budgeting are similar to previous methods.
- Schematic design is produced in conjunction with the builder. Costs are more closely associated with the design decision.
- After the design is agreed to the design/builder delivers the schematic design drawings and a build proposal – lump sum or cost plus.
- The budget and/or design is modified if required and a contract for Phase II is signed for a lump sum. The actual cost of the project is known at the end of schematic design (3 to 5 months earlier than the traditional methods).
- The design/builder prepares the permit and construction documents based on the build proposal.

Pros
- Is a collaborative team approach
- Project cost are known earlier
- Can be either a program or cost driven project
- Single source of responsibility, no finger pointing
- Owner's time level is reduced

Cons
- Perception of lack of checks and balances – Potential for abuse
- Potential for problems from an inexperienced design/builder
- Owner's control is reduced

CONCLUSION

The more detailed information that you can obtain the more precise your budgets will be. There will be a lot of people putting their hands in your pockets; try to make sure you have the majority of these people accounted for. You certainly do not want to have to go back to the well at the end of project to cover something that could have been accounted for earlier. Make sure that if someone quotes a dollar per square foot number, make sure you understand what exactly that entails. Typically the construction cost account for an average of 45% to 60% of the total budget.

Deciding on which building method to use largely depends on the following:

- How much involvement you want
- How early you want to know what things are going to cost
- Trust the professionals that you want to work with, but stay apprised as the project develops

Selecting professionals that have experience in the system that best suits you, as well as experience in animal hospital projects.

Table 1. Design/Builders Budget

Description	**Unit Costs**	**Quantity**	**Line Cost**	**Subtotal**
Architectural Documents Budget				
Heated Clinical / Hospital Area	13.00	5,500	71,500.00	
				71,500.00
Engineering and Consultants Budget				
Structural Engineering	1.25	6,000	7,500.00	
Electrical Engineering	1.00	5,500	5,500.00	
Mechanical (HVAC) and Plumbing Engineering	1.25	5,500	6,875.00	
Civil Engineering	1.00	20,000	20,000.00	
Interior Design	1.00	5,000	5,000.00	
Boundary Survey and Aerial, Title/bank Survey	0.00	1	0.00	
Geotechnical	1.00	3,500	3,500.00	
Landscape Architect	1.00	3,500	3,500.00	
				51,875.00
Construction Budget				
Heated Clinical / Hospital Area	170.00	5,500	935,000.00	
				935,000.00
Fire Protection				
Wet Sprinkler Allowance	5.00	5,500	27,500.00	
Fire alarm -Allowance	1.00	5,500	5,500.00	
				33,000.00
Enhancements				
Architectural Copper Roofing	12.00	3,000	36,000.00	
				36,000.00
Site Development Budget	17.00%	1,004,000	170,680.00	
				170,680.00
Builders Overhead & Profit	1,381,976.47	0.15		207,296.47
Area Modifier	5.00%	1,174,680	58,734.00	58,734.00
Taxes		898,284.71	5.50%	49,405.66

			Total Budget	**$1,613,491.13**

Table 2. Owner's Managed Budget

Description	**Cost**	**Quantity**	**Line Cost**	**Subtotal**
Owner's/Bank Contingency	10.00%	935,000	93,500.00	
				93,500.00
Business Systems				
Phones, equipment & wiring	15,000.00	1	15,000.00	
Intercom, paging and Music	6,000.00	0	0.00	
Computers, equipment and wiring	10,000.00	1	10,000.00	
Monument & Building Signs, Logos and Advertising	15,000.00	1	15,000.00	
Intrusion alarm	8,000.00	1	8,000.00	
Video systems (Wire only)	5,000.00	0	0.00	
				48,000.00
Owner's Land Costs				
Land Costs	250,000.00	1	250,000.00	
				250,000.00
Banking and Legal Costs				
Bank Inspections	175.00	6	1,050.00	
Construction Financing (9.25%)	1,000,000	7,708	46,250.00	
Insurance-Property Insurance	1.00	6,000	6,000.00	
Insurance-All Risk/Builders Risk	1,000,000	0.005	5,000.00	
Appraisal	5,000.00	1	5,000.00	
Attorney's Fees	2,500.00	1	2,500.00	
Title	5,000.00	1	5,000.00	
Loan Origination Fees (1-2%)	2,163,281	1.50%	32,449.22	
				103,249.22
Impact Fees, Developmental, Use or Expansion Fees				
Traffic	1.00	7,500	7,500.00	
School Fees			0.00	
Streets & maintenance	1.00		0.00	
Sign fees	0.00		0.00	
Utility expansion fees	1.00	2,500	2,500.00	
Water, electric and gas meters	1.00	5,000	5,000.00	
				15,000.00
Medical Equipment				
Medical hoses Oxygen (Owner's Gas Supplier)	75.00	10	750.00	
A/E Hoses	210.00	7	1,470.00	
View Box illuminators	135.00	2	270.00	
Exam Lights	1,200.00	4	4,800.00	
Surgery Lights	1,800.00	1	1,800.00	
Oxygen/Recovery cage	0.00	0	0.00	
Microscope	1,730.00	0	0.00	
				9,090.00

Stainless Steel Equipment				
Cat Condos	500.00	12	6,000.00	
Runs Ward	1,500.00	10	15,000.00	
Runs Outdoor	2,000.00	0	0.00	
Luxury Runs (doors and finishes)	1,500.00	0	0.00	
Cages Canine Ward	450.00	10	4,500.00	
Cages Feline Ward	450.00	12	5,400.00	
Runs Isolation Ward	1,500.00	1	1,500.00	
Drying cage	6,000.00	0	0.00	
Tub Tables	2,400.00	2	4,800.00	
Groom Tubs	2,300.00	1	2,300.00	
Surgery Table	2,600.00	0	0.00	
Lift Table	2,400.00	2	4,800.00	
Exam Tables	500.00	0	0.00	
Groom table (drawers)	400.00	0	0.00	
Recessed Scale	750.00	1	750.00	
				45,050.00
Miscellaneous				
Window Coverings	0.00	0	0.00	
X-ray equipment	60,000.00	1	60,000.00	
X-ray (relocate)	1,500.00	0	0.00	
X-ray Shielding and certification	0.00	0	0.00	
Dental X-ray (Digital)	10,000.00	1	10,000.00	
Office and Facility furnishings	10,000.00	1	10,000.00	
Miscellaneous	0.00	0	0.00	
				80,000.00
Appliances				
Freezer	500.00	0	0.00	
Refrigerator	600.00	1	600.00	
Dishwasher (Lounge)	400.00	1	400.00	
Commercial Washer (35 lb, soft mount)	3,500.00	1	3,500.00	
Commercial Dryer (50lb, gas dryer)	4,000.00	1	4,000.00	
Residential Washer	500.00	0	0.00	
Residential Dryer	750.00	0	0.00	
Stove/Range	750.00	0	0.00	
Garbage Disposal	150.00	1	150.00	
Microwave (lounge)	500.00	1	500.00	
				9,150.00
Total Owners Managed Budget				$653,039.22

FLOORING – WHAT WE ARE SEEING IN THE FIELD

Sean Campbell
Vice President of Construction
CMP, Inc., Albuquerque, NM

OBJECTIVES

This article provides an overview of the positives and negatives of flooring types that may arise in the pre-installation, installation, or finished appearance of various flooring types.

- Largest single interior material expense
- Installation cost is usually in inverse proportion to maintenance expense
- Proper selection is critical for odor and pathogen control, as well as the quality of final installation

SELECTION CONSIDERATIONS

- Based on room requirements
- Durability
- Aesthetics
- Maintenance requirements
- Bacterial resistance
- Abrasion, stain and slip resistance
- Physical comfort
- Installation versus life cycle cost

FLOOR TYPES

- Concrete
- Continuous membrane
- Sheet goods
- Tile

CONCRETE FLOORS

- Inexpensive for non-wood frame floor structures
- Very durable, abrasion resistant
- Can be colored or stained after placement
- Requires a sealer/hardener to help prevent staining
- Surface prep is critical for proper sealing
- Is upgradeable to another finish later
- Very low maintenance, depending on finish
- Potential for cracks and aesthetic blemishes

Concrete Field Issues

- Rarely is installed perfectly flat
- Two types of concrete, one that is cracked and one that hasn't cracked yet
- You can control cracking to some extent with expansion and control joints, but there is always a potential for cracking
- Typical cracking is shrinkage or hairline cracks
- Large cracks typically are generated from poor sub subsurface preparation, settling of heaving of soils
- Staining and damaged during construction, oils, cokes, markers, and objects being dropped
- Protecting concrete floors from staining typically is accomplished with construction paper or tarps, which adds to the cost of the system, which has to be maintained for the duration of the project.

CONTINUOUS MEMBRANE SYSTEMS

- Epoxy Systems
- Urethane Systems
- Methyl Methacrylate

These systems are typically troweled and rolled-on systems, which can be installed over wood or concrete systems. They can be clear or opaque. Opaque adds color and texture to improve appearance. Can be flashed coved up walls for a true seamless installation and have relatively inexpensive cost to maintain.

Types of Membranes

Epoxy Systems

- Polyamide and one part Epoxy part sealers
- Troweled Epoxy floors
- High build and low build systems
- Thickness depends on performance requirements
- Use Quartz or other aggregates for abrasion resistance
- Aggregates can be colored to improve appearance

Methyl Methacrylate

- Penetrates and bonds to concrete
- Can be applied to wood structure with a proper substrate
- Non-staining, non-yellowing
- Moisture proof, resistant to weathering

Urethane Systems

- Clear and pigmented systems
- Weaker adhesion to concrete than other systems
- Yellows with exposure to sunlight
- High abrasion and chemical resistance
- Not advisable when concrete has moisture present

Membrane Field Issues

- Cracking in the concrete will telegraph through
- Installation process is critical to the final appearance of the system
- Manufactured on site and is prone to human error in application that may result in bad appearance
- Time frame for installation is lengthy
- Entire projects may need to be shut down for installation
- Air born dust will settle in uncured materials
- Can be easily tracked onto other surfaces if product has not been cured
- Very difficult to remove from other materials, painted gyp board, wall coverings, etc
- Slab prep can be extensive for adhesion, sand blasting and sealers may be needed, which can add to the cost
- Biggest issue is the final appearance. “My floor does not look like the 3 x 3 sample you gave me.” You need to have installer provide larger sample

manufactured on site and not small sample made by the manufacturer in a controlled environment. Remember the human element during installation will always play into the way final product will look.

SHEET GOODS

- Vinyls
- Linoleum
- Rubber products

Sheet goods are manufactured in a controlled environment and less likely to end up looking different than the 3 x 3 sample you first look at. Typically come in 4- to 6-foot wide rolls or cut sheets, which means seams. Most sheet goods require regular maintenance but they have an initial lower cost for installation. They can be flash coved or sanitary bases can be used

Vinyls

- 6-foot wide rolls
- No-wax finishes available but still require regular maintenance
- Heat or chemically welded seams
- Resilient material is easier on the feet
- Provides some acoustical value

Linoleum

- All natural materials, recyclable
- Can be sealed for a gloss finish or left natural, unsealed may stain
- Very abrasion resistant

Rubber Floors

- Non-absorbing, non-staining
- Slip resistant
- Low maintenance
- Resilient material
- Limited color choices
- Flash coved or pre-formed coves

Membrane Field Issues

- Tremendous amount of subsurface prep is needed to control moisture
- Manufactures have lowered moisture content requirement in slabs to protect themselves from warranty callbacks
- Vapor barriers need to be installed under slab
- Topical sealers are usually required to be applied to concrete slabs
- Adhesives, which have been changed to a water based material, are prone to failure if moisture is present, resulting in delamination and/or bubbling
- Seams have had potential for opening, usually due to shrinkage in sheet material (vinyls)
- Inside and outside corners are hardest to detail, sometimes resulting in messy looking applications
- Color selection of product will potentially promote a dirty appearance

TILE

- Ceramic Tile
- Porcelain Tile
- Quarry Tile
- Grouts

Tile products have a much greater aesthetic value than the flooring product mentioned. Materials that are used in conjunction with these tile products have a larger determination of the overall performance of the floor. No matter what type of tile you use, you should use an epoxy grout on horizontal surfaces. Tiles in general have a low comfort level and have very little acoustical value if any. Tile products can be used in all areas of a hospital but tend to be used in the client accessed areas.

Ceramic Tile

- Excellent appearance
- Many styles and colors available
- Tile finish is on the surface only
- Tile body is not non-absorbing
- Glazed tile must be matte finish for slip resistance on floors, gloss on base or walls
- Is prone to chipping at corners – not as strong as porcelain tile
- Can go over wood or concrete floors
- Avoid types requiring sealer

Porcelain Tile

- Very strong and abrasion resistant
- Most are completely non-absorbing
- Color is integral throughout the body, not a surface coating
- Is more expensive than ceramic
- Matte and gloss finishes available
- Best selection for entry / waiting areas

Quarry Tile

- Clay based (non-vitreous) products, not moisture proof, require sealers
- Higher maintenance requirements, lower initial costs
- Solid colors most common
- Pavers are commonly exterior finishes, set in sand bed

Grouts

- The weak link in a tile installation
- Very difficult to keep standard latex modified types from staining
- Epoxy grout is best: non-staining, anti-microbial
- Epoxy is more difficult to install – use experienced installers only
- Must cure a minimum of 3 days without traffic – can cause a schedule bottleneck at project completion

Tile Field Issues

- The larger the spacing of tiles the more likely there will have an uneven appearance

- String or chalk lines need to be established for straight applications
- Use spacers when setting tiles
- Purchase materials from the same die lots. Color variation is noticeable
- Proper mixing of grouts should strictly be followed. Hand mix, no high speed mixing should be used. The faster one mixes the faster the material sets up, making it more difficult to apply
- Use proper cleaning procedures. Epoxy grout once it has setup is very difficult to remove
- Avoid having other construction taking place during grouting
- Use proper curing time. Tracking of uncured grout will be a problem later
- Neatness of the installer will produce a much better application. Avoid grout on surfaces that it is not intended: wall coverings, painted gypsum board, doors, etc.
- All grouts tend to sag, leaving a trough for fluids to set in. An experienced installer will minimize the depth.
- In almost every project, we have a client that calls and says my epoxy grout is staining. Most of the time it is due to improper cleaning. If you use dirty water to mop, when it dries the dirt will be left on top of the grout.

CONCLUSION

There will always be concerns as to what product you should use and in which location. The deciding factors will be determined by aesthetics, cost, ease of installation, performance, and maintainability. With all types of flooring having their different issues, one common element should not be overlooked. "The Human Element"—your floor is only as good as the person who installs it. Due diligence is a must for research, sub floor prep, installation and maintenance.

MECHANICAL, ELECTRICAL, AND PLUMBING SYSTEMS

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These three critical veterinary building systems are usually designed by the architect's engineering consultant, either as an in-house employee or a subcontractor. Due to the close interrelationship between these systems, it can be one, two or three individual engineers responsible for the design. Most commonly, a mechanical engineer designs the heating, ventilation, air conditioning system (HVAC) and the plumbing system. A separate electrical engineer usually designs the power and lighting systems as well as telephone and network system layout and outlet locations. Typically, the mechanical/electrical engineering costs will be included in the architect's scope of work and fee. This allows closer interdisciplinary coordination than if the owner retained and coordinated the professions.

THE MECHANICAL BUILDING SYSTEMS

Plumbing Systems

Several different systems comprise the plumbing system for which the mechanical engineer has responsibility:

1. Domestic water system
2. Sanitary sewer (drain, waste and vent)
3. Gas (natural or LP)
4. Medical gases (oxygen, nitrogen, compressed air, medical vacuum, nitrous oxide, etc.)
5. Central vacuum cleaning
6. Anesthesia evacuation
7. Storm sewer (when not completed by the civil engineer)
8. Fire protection (sprinkler)

The plumbing systems in the Veterinary Hospital Project may be installed by one or several plumbing subcontractors. On larger, more complex facilities containing numerous of the identified systems, specialist subcontractors may be retained for each individual system. National and local plumbing codes will govern installation and design, as will National Life Safety Codes and some OSHA requirements.

Domestic Water System

This system brings potable water from the municipal supply or private well into the facility and distributes hot and cold water to plumbing fixtures. Typically, well and well equipment designs will result in additional design fees above the norm.

Tips

1. Keep utility runs from main to building as short as possible. Check main size and pressure availability.
2. Typical veterinary services range from 1" to 2". Pay attention to size. Meter size (service size) can impact fees from the city by $10,000 or greater.
3. Consult with the municipality regarding utility expansion charges, franchise fees, etc. These can be considerable and are the owner's responsibility.
4. Do not run piping in noninsulated spaces like attics, or other freeze-prone locations. Try to keep runs in accessible areas for future renovations.
5. Use a hot water recirculating pump in hospitals over 5000 SF.
6. Insulate all pipes – hot and cold.

Sanitary Sewer System (Drain, Waster and Vent)

This system carries waste from plumbing fixtures to the municipal sewer or private septic tank. Septic tank design and installation is typically an additional cost item, as municipal sewer systems are the norm. These systems can be plastic or cast iron pipe, as required by local codes. Our preference is plastic, as it performs better, is more economical and allows greater flexibility.

Tips

Use prefabricated, presloped, manufactured, modular trench drain systems in runs. Site built concrete is too unreliable.

1. Hair traps and strainers should be used on all fixtures where hair might be present.
2. Provide adequate clean outs for system maintenance.
3. Provide covers and strainers on all drains to remove largest waste manually.
4. Avoid use of abrasive snakes to clean plastic drain lines.

Gas System (Natural or LP)

This system provides fuel gas-to-gas burning appliances such as furnaces, clothes dryers, water heaters, etc. The system consists of a yard line from the meter or fuel tank to the building and distribution piping to appliances or fixtures.

Tips

Natural gas is typically a more economical and efficient fuel than electricity. When available, gas is usually the best alternative. Locales where oil is used as fuel should investigate LP gas as an improved, cleaner fuel.

1. Gas piping is typically black steel. Provide shut off valves at every appliance as well as an easily located building shut off.

Medical Gas Systems

These systems include compressed gases (oxygen, air, nitrogen, nitrous oxide, etc.) supplied from tanks or generators, as well as medical vacuum (suction) systems. Normally these services are delivered through welded copper pipe, regulated at gauged manifold and available to use at wall or ceiling outlets. Medical vacuum is created by a vacuum pump and supplied either directly from the pump or stored in a pressure vessel and replenished by a vacuum pump.

Tips

1. Use manual oxygen tank transfer manifolds. Automatic transfer allows you to "forget" to switch over and replace spent tank(s). You will also save money.
2. Select an oxygen system that has a low-pressure alarm.
3. Keep oxygen tank closet on an outside wall for easy safety venting.
4. Select between wall or ceiling outlets thoughtfully.
5. Consider using a specialist subcontractor for this work.
6. Medical vacuum systems will be located in a separate area from gases. Place in a remote, soundproof location, as pumps are noisy.

Central Vacuum Cleaning

This system provides centralized vacuum for general housekeeping and hair cleanup for procedures and grooming. Some systems incorporate anesthesia and laser smoke evacuation.

Tips

1. Locate power unit in a remote, soundproof location, as central to the outlets as possible.
2. Check standard hose length. Be sure all corners of all areas can be reached. Design for some overlap.
3. Use "dust pan outlets" on floor at waiting, lobby, grooming and surgery prep. These facilitate a quick broom sweeping.
4. Do not over allocate outlets or you may unnecessarily increase motor size and system cost.
5. Purchase more than one hose unit. You may want a long "housekeeping" hose and a short "procedure" hose.

Anesthesia Evacuation

This system provides a constant, low-level vacuum when attached to the anesthesia machine to scavenge waste gases. These systems are vacuum pump driven and can be constant or pressure vessel recharged.

Tips

1. While almost always ceiling located, outlets can be wall mounted, which removes the "corrugated hose coil" from the ceiling.
2. If using a vacuum pump, always on system, put power on wall switch with pilot light in central, easily seen location.
3. Only purchase proven, tested, certified systems. Many systems have too much variance, resulting in poor anesthesia control.

Storm Water Sewer System

This system gathers rainwater and runoff, collects it to a catchment system, and redirects it to a municipal system or retention pond. More often than not, this system is completed by the civil engineer in contract directly with the owner.

Tips

1. Roof drain, gutters and downspouts tie into this system.
2. Parking lots and other "hard, non permeable" surfaces must be designed to divert to this system.
3. Footing drains and foundation drains should tie into this system.
4. Sanitary uses cannot tie to storm use. Floor drains, runs or exterior runs cannot tie to the storm system.

Fire Protection System

This system, usually is specified by the plumbing engineer for performance, and designed by a specialty subcontractor. Your requirement by code for this system will be a result of building size and construction materials used. Local fire codes often dictate system use as well.

Tips

1. A full coverage system requires either a large (4"+) water main, or a large storage tank.
2. A large (expensive) standpipe and closet about 30 SF is required for the service equipment.
3. Systems cost $5 to $6 per square foot, on average.
4. Partial systems for specific coverage (wards, mechanical rooms, runs, boarding areas) are possible.

HEATING, VENTILATING AND EXHAUST SYSTEMS (HVAC)

In the animal hospital, these three systems are designed to work together to maintain occupant comfort as well as serve important functions in acoustic and odor control. Two main choices are available when selecting heating/cooling systems – forced air and hydronic.

Forced air systems heat and cool air, then send it through distribution ductwork to individual rooms. Hydronic systems heat and cool liquid median, distribute it to radiating units, which in turn, condition the occupants and air in the room. Hydronic cooling systems use ductwork and forced air cooled by the liquid median. Because of the added HVAC function in animal hospitals to provide acoustic and odor control, we recommend forced air systems. These allow us to use one unit for each zone, resulting in better zone tempering, ability to pressurize for zone odor control, and to supply fresh air as needed to replenish exhausted air.

Tips

1. Provide one unit for each zone.
2. Do not penetrate ductwork between zones to maintain acoustic separation.

3. Use space over suspended ceiling for ductwork distribution. Maintain 24"-30" clear open space to beams, rafters, etc.
4. Use metal, insulated ductwork.
5. Use programmable electronic thermostats.
6. Design for the following ventilation rates (air changes / hour):

Area	HVAC System	Exhaust System
Waiting/Reception	6-8	
Treatment	6-12	
Isolation	6-12	12-16
Runs / Wards	6-12	12-16

7. Use filtration that can eliminate particles in the 1 to 5 micron range. Standard 1" to 2" fiberglass filters cannot do this. Electrostatic and HEPA filters can achieve this. Investigate costs of your designers choices.

THE BUILDING ELECTRICAL SYSTEMS

Typically designed by an electrical engineer within the scope of your Architect–Owner Agreement, these systems must be closely coordinated with both the architects design elements, the Mechanical Engineering Systems and the Owners Equipment. Three major areas comprise the Electrical Engineers Systems:

1. Power
2. Lighting
3. Data and Telephone (system layout)

Electrical Power Systems

Two primary elements comprise the building power systems.

1. Service
2. Distribution

Service Entrance

This element includes all the equipment from the utility company lines to the building electrical panels. It can include a transformer, overhead or underground primary conductors, the meter with shut off switch, and differing configurations of panels. Animal hospital services range from 200 to 800 amps, single or 3-phase service. 400 amps is a typical service for hospitals under 7000 SF, but each is specifically sized based on that practice unique requirements. Three-phase service is almost always preferable where available.

Distribution

The distribution system consists of the electrical panel boards, of which there are typically two, one for power systems and one for lighting systems and the wiring to boxes and fixtures. Systems below 400 amps will often combine into a single panel board. Often, a separate, fused cabinet with shut off switch is provided for x-ray equipment. Panelboards may be fused or circuit breakers, depending on fault current rating needs. Circuit breakers are most common, if for no other reason than increased safety and ease of maintenance for the hospital staff. Wiring extending from the panel boards may be anything from residential style romex (though rare), non-metallic (plastic) shielded conductors, metallic shielded armor cable to emt (thinwall) conduit. Cable runs terminate in outlet boxes for duplex receptacles or equipment connection. Runs to light fixtures typically have no box, with wiring right to the fixture for connection.

Tips

Locate electrical panels in an accessible location. A service corridor where nothing will be stored in front of them is better than a storage room that will render them inaccessible.

1. Typically, 3 feet of wall space is needed per panel, with 3 feet of clearance in front of the panel.
2. Provide ground fault interrupting (GFI) outlets at all areas that can get wet – treatment, bathing, grooming, runs, etc.
3. Provide 20-amp dedicated circuits for equipment like cage dryers, drying cages, ICU units, etc.
4. Consider ceiling outlets in locations such as over surgery tables, grooming / surgery prep (cord reels), etc.
5. Consider plug mold strips for ICU, lab and other locations where multiple outlets for equipment may be needed.

Electrical Lighting Systems

Three types of lighting must be designed in the veterinary facility:

1. General lighting
2. Task lighting
3. Accent lighting

General lighting provides general, overall illumination throughout the facility. This is most often accomplished with 2x4 fluorescent fixtures in a suspended ceiling grid. A wide variety of lens choices are available to control glare and direct the pattern and spread of the illumination. Indirect fixtures are also used to provide light by reflectance, which provide an overall illuminative effect eliminating direct light glare. In addition to a higher quality of general light, areas where computers are used benefit from the elimination of screen glare. New energy efficient T8 or T5 lamps are recommended, as are electronic ballasts, both for energy efficiency and hum elimination.

Task lighting is used to increase illumination for specific tasks. Surgery lighting is the most common example of this. Treatment tables, dental area, exam tables and special procedure areas often receive task lighting as well. These fixtures are most commonly incandescent lighting.

Accent lighting is used to highlight or focus attention on a building or business feature. Examples are retail displays, logo walls, artwork and information displays. This lighting is often accomplished with track lighting, wall washer fixtures, focusing cans, and suspended low voltage halogen fixtures.

Lighting levels are expressed in footcandles, which is a unit of measurement related to brightness. Tasks requiring close visualization should receive about 100 footcandles. These can include exams, treatment areas and record notation. Mid level tasks like reception, office areas, and lounge should receive 50–75 footcandles. Tasks or areas not needing visual scrutiny like wards and runs should receive 20–40 footcandles. Two level lighting can also be used to allow manual switching "up" from a low ambient light level to a higher footcandle when required.

Tips

1. Consider occupancy sensors for areas used in varying amounts throughout the day. Movement turns on or keeps lights on, lack thereof turns lights off.
2. Use a variety of 2x4 fluorescents to meet the specific room needs. Indirect fluorescents can be used around computers; Parabolic lenses should be used to direct light straight down; Prismatic lenses should be used to spread general illumination.
3. Mix fixtures. Use a combination of 2x4 lay in, surface mounted, recessed cans, tracklite, wall sconces, pendant, etc. to suit the needs of that space.

EXTERIORS MATTER: LANDSCAPING, PARKING, ENTRIES AND CURB APPEAL

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CURB APPEAL

When a realtor prepares to sell a home, he or she often attempts to improve its appearance as viewed from the street. They call this "curb appeal." There is even a current television program in which experts makeover an unattractive residence using tricks-of-the-trade.

The outward appearance of your facility creates the first and last impressions that clients or your community have of your practice of veterinary medicine or the professionalism of your boarding facility. The exterior design of a building, sign, drives, parking lot and landscaped areas must not be left to chance. The careful design of these features results in the all-important image projected by your hospital or boarding facility.

CRITIQUE YOUR PRESENT OR PROPOSED FACILITY

When is the last time you viewed your hospital or boarding kennel through the eyes of your clients? Over time, most animal care facilities, although initially well designed, need to be updated. You should critically analyze your current or proposed building and grounds with your hospital's image in mind.

If your facility is an existing building, take photos of all areas of your site and hospital to review and analyze (after hours and away from the clinic). Looking at photos tends to allow a more impersonal view of your facility. They will often point up features, both good and bad, that would have been overlooked during a physical walk-through.

If you are building a new structure, analyze the site plan and building elevation drawings and imagine you are driving onto your site and walking into your building.

After your review, make a list of suggestions for improvements, future repairs, or alterations that would help fulfill your practice goals or image. This list will assist you, the practitioner, in correcting design errors or omissions or in prioritizing repairs and projects that will greatly improve your hospital's function and appearance.

The critique should include:

- A statement of what type of image you desire (for example, warm and homey or sophisticated and clinical)
- Critique of site plan (access, signage, parking, landscape, building street appeal)
- Assessment of building's entry (Can you find it from parking areas? Traffic flow?)
- Review of overall building esthetics
- Critique of exterior building finish materials
- Evaluation of landscape design and materials

SITE PLANNING

When planning your building, site, and landscaping think of the outdoor areas of your facility as another room. Design the site with regard to traffic flow, necessary or desired features and amenities and appearance. Do not let the design of your building's exterior features be an after-thought.

When planning your site, consider the following:

- Marked pet urination area for pets entering hospital
- Easily located building entry from parking area
- Exterior lighting requirements
- Location of utility services, required meter locations
- Service or delivery requirements, trash pick-up or dumpster location
- Sign design (veterinary association regulations and city ordinances)
- Landscape requirements (city ordinance)
- Expansion room for future growth of hospital
- Integrate building design and site design

ELIMINATING NOISE AND ODOR ISSUES

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FIRST IMPRESSIONS ARE VERY IMPORTANT. BY THE WAY, WHAT IS THAT SMELL?

Offensive sounds and odors are a result of normal hospital activities. In many older hospitals they are an unfortunate fact of life. In today's state-of-the-art hospitals this is not the case. Clients expect and appreciate it; you and your staff deserve it. Sound and odor control is not an option, it is mandatory.

NOISE CONTROL

There are five design principles that can be utilized, hopefully in concert, to mitigate unwanted noise within a building. These principles are isolation, absorption, dissipation, masking and design of the heating, ventilating and air-conditioning system (HVAC system).

Isolation

During the design of the hospital's floor plan is the time to start thinking of noise control. Locating noisy areas within the building plan to group and separate them from quieter hospital areas is the first step toward sound control. Sound is transmitted generally in a straight line. Creating an indirect path leading to sound-generating areas is good practice. Solid doors with weather-stripping should be used to provide access through sound walls. In addition, sound walls should extend above the ceilings to the roof deck or other structural block to prevent "flanking" or movement of sound up and over walls then dropping down to the next room.

The next isolation technique is to separate the noise generating areas from other hospital areas by walls without unnecessary openings and of sufficient density to greatly reduce the transmission of sound. The rate that sound is transmitted through objects is measured by a Sound Transmission Coefficient (STC) rating. A sound wall with an STC rating of near 50 is economically feasible. This means that this wall will stop 50 decibels of sound. A dog barks in the range of 100 decibels. This is why our design principles must be used together to increase sound absorption.

Absorption

Absorbing unwanted sound as close to the source as possible before it can spread to other areas is obviously desirable. Unfortunately, the typical sound absorbent material is usually rather soft, porous, and not easily cleaned. This makes it a poor material for most areas where animals are housed. Normally the ceiling of these areas is the surface relied on for sound absorption. In looking for materials to absorb sound you are looking for materials with a high Noise Reduction Coefficient (NRC) rating. An NRC rating of 1.0 means that the material rated will absorb 100% of the sound striking the surface. Ceiling tiles have approximately a .75 NRC. In contrast, a concrete block run wall and concrete floor have an NRC rating of 0.1.

Dissipation

Another way to control sound is to allow it to dissipate. In a large space, sound can die off before it hits a wall and bounces back. In the outdoors where there are no walls, sound will die off at the inverse square of the distance. This means that sound will dissipate to nothing in a very short distance. In an animal hospital it is virtually impossible to create a space large enough for this dissipation of sound to occur naturally. By increasing the height of a room and adding as much absorptive material as possible, you can move toward this goal.

Masking

Masking is the last resort in sound mitigation. The principle is basically to cover or mask the unwanted noise with a more pleasant sound. We are all familiar with Muzak or other sound systems that utilize music for this effect. Masking is much more effective covering a consistent noise. It is not particularly effective in masking sporadic barking.

HVAC System Consideration

HVAC ducts penetrating from one sound-controlled zone to another obviously can be avenues for sound or noise leakage. Eliminating ducts passing from one zone to another can control this transmission source. A ceiling penetration by a diffuser or grille will allow sound to migrate to another room within the same sound control zone. There are methods to control noise transmission when ducts must pass through sound walls between zones. These systems are costly and should be avoided where possible.

ODOR CONTROL

There are only three principles that can effectively control odor:

- Cleanliness
- Exhausting unclean air and introducing fresh air
- HVAC zones and space-pressure relationships

Cleanliness

Odor control can best be accomplished by eliminating the source. Frequent cleaning of all areas of the hospital is the first and most obvious step in control of odor. Using easy-to-clean finish materials and providing conveniently located service sinks, mop buckets, etc. is especially important. Properly designed runs with easy to clean surfaces and drains are imperative.

Exhausting Unclean Air and Introducing Fresh Air

One way to control odor in a facility is to exhaust unclean air. Exhaust fans should be provided for the following areas:

- Exam rooms

- Treatment
- Laboratory
- Grooming
- All toilets
- Canine wards, boarding and runs
- Feline wards and boarding
- Isolation
- Darkroom

The HVAC systems should be designed to bring fresh, odorless outside air into the building at all times. The amount of outside air that is introduced is calculated in numbers of air changes per hour. We recommend utilizing a mechanical engineer, experienced in the design of animal care facilities, for the design of these systems. We recommend eight to ten air changes per hour in animal housing and treatment areas.

HVAC Zones and Space-Pressure Relationships

We recommend that the hospital be divided into HVAC zones. These zones generally contain and define functional areas of the hospital. The most basic concept is the traditional "front, middle, back" configuration. The front is the client area, including the waiting, reception, and exam areas. The middle is the medical procedure area consisting of laboratory, pharmacy, treatment, imaging, and surgery areas. The back contains the patient wards, runs and utility support spaces. Each of the three zones would have its own, independent, HVAC system with separate return air, filter and thermostat.

If you supply more air to a zone than you exhaust, it will create a positive pressure. If you exhaust more air from a zone than you supply, it will create negative pressure. In a properly designed HVAC system, the "front" zone would have the most positive pressure and the "back" zone the most negative pressure. Thus any air leaking between zones would move from the most odor-free zone to the least odor-free zone.

Today's animal hospital is expected to be a modern, fully equipped, medical facility. Obviously, every effort should be made to control the negative impressions and unprofessional practice environment created by unwanted noise and odor.

TRENDS IN HOSPITALIZATION AND BOARDING AREAS

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In recent years, much time and energy has been invested in designing veterinary facilities that are inviting, open, and client friendly. These beautiful, state-of-the-art facilities emphasize efficient hospital operations and house the latest in medical equipment. Still, even in today's progressive facilities, one important hospital area is often overlooked. Sadly, the area dedicated to the hospitalization or housing of animals is often designed as it was two decades ago. While most veterinarians insist that the animal housing that they install is easily cleaned, durable, secure, and functional, some still want to house the maximum number of animals in the least amount of space. However, in today's most progressive facilities, the design of animal enclosures is changing from caring for the maximum number of animals with the least amount of effort, to including consideration of the behavioral, biological, psychological, and social health of the animals.

ANIMAL HOUSING OVERVIEW

Veterinary facilities house animals for one of two purposes. Sick or recovering animals are monitored in inpatient hospital wards. IN addition, many animal facilities offer on-site boarding accommodations as an additional service to their clients, and the surrounding community.

A variety of species may need to be accommodated, depending on your local market, practice focus, or area of interest. Each species has specific requirements depending on its size, physical needs, environmental control requirements, and hospital operational policies. A wide range of variables is present within each group. Canines range in size from miniatures to giants. Felines can be grouped individually or together when in the same family. Exotics require some of the most specific accommodations and have the widest diversity of needs, not excluding farm animals which can be pets, athletes, or food animals.

- **Inpatient Hospital Wards**
  - Critical Care
  - Intensive Care
  - Intermediate Care
  - Discharge
  - Isolation
  - Specialty Specific

- **Boarding Accommodations**
  - Standard
  - Luxury

HOUSING FOR DOGS

Traditional runs and cages can create stress and promote undesirable behavior, such as barking, fence fighting, lunging at gates, and soiling the enclosures.

The principal goal of performance-based animal enclosures is to decrease the stress level in the animals being held. Well-designed enclosures can appreciably reduce the stress level for individual animals, which promotes a calmer atmosphere for the other animals and staff alike.

Researchers say that the single most effective factor in reducing the stress of captive animals is to provide them with a choice of environment. This could include separate resting, exercise, hiding, feeding, and defecation areas. Providing a hiding space somewhat like a den, or a "defensible" space, allows a dog to feel secure. It can be under a resting bench, behind a partial wall, or even in a temporary crate. Raised platforms allow for a vantage point. Being stuck at the bottom of a concrete box without the opportunity to see what's going on outside the enclosure can add to the stress of confinement.

Appropriate enclosures need to be based on the individual sizes and species of the animals being housed. The standard one-size-fits-all approach to run design ignores these differences. What is comfortable for a Maltese won't work for a Great Dane. The shape of traditional runs also contributes to discomfort. In the typical long, narrow run, dogs can't move and circle in the same way they would in a free environment. When individually housed, this is not a significant concern, but when another dog or a staff member is in the run, some dogs will feel trapped and display abnormal levels of aggression. You see the same dynamic in play when dogs pass each other in narrow hallways. A square enclosure works better than a long narrow run for meeting spatial needs.

Conventional wisdom has it that if animal enclosures are arranged so dogs cannot see each other, agitation and barking will be minimized. However, some studies have indicated that visual contact did not necessarily increase vocalization. If dogs seek out and derive some benefit from visual contact, perhaps radical changes are necessary to traditional enclosure design. Enclosures built with extensive use of glass, built-in lookout perches, and clustering units can offer increased visual contact and interest. Another aspect for reducing stress is to create a homelike ambience in the holding areas. At a minimum, this means creating a ward area that is light and spacious with access to a soft, warm surface for resting. Long corridors where dogs have to "walk the gauntlet," cages, and bars should be avoided and replaced by glass, ceramics, and other equally cleanable surfaces.

HOUSING FOR CATS

Design goals for cat enclosures include providing adequate space for freedom of movement and room for the cats to fully stretch. Furnishings should include resting platforms, elevated vantage points, climbing frames, and raised walkways. Kitten enclosures should be provided with ramps. Ideally, a variety of textures should be used, including soft resting surfaces. Many cats will sleep in their litter boxes if a more attractive alternative is not provided.

While some studies indicate that enclosures should be designed to allow cats to see each other, hiding places are also critical in reducing overall stress levels in confined cats. Studies indicate that a generous allocation of space reduces the stress level in cats. The ideal cat housing area allows three square feet per cat and at least one and a half feet between functional areas, such as perches and the feeding and litter box areas.

Significant advances have been made in commercially available cat housing in recent years. Cat condos have been designed to give cats three-dimensional space and a choice of environment. Some of the larger units allow for separate resting platforms, feeding and litter box areas.

COMPANIONSHIP

Safety and disease control are critical for the animals in your care. However, the detrimental effects of isolated housing should also be considered. Social isolation is stressful, especially for dogs that are pack animals by nature. Stress renders animals more susceptible to disease and prolongs the recovery time of sick animals. While housing two unacquainted dogs in the same enclosure always involves a certain amount of risk, temperament and breed assessment prior to social housing can minimize the chances of aggression. Stressed and/or bored dogs can do incredible damage to their environment. Given the right type of enclosure, companion housing has a calming effect on many dogs and also facilitates exercise and play. Being with another dog enriches the environment with visual, auditory, and olfactory stimuli that reduces boredom.

EXERCISE

Most dog housing is designed to minimize labor cost by eliminating as much animal handling as possible. As a consequence, most staff time is spent cleaning up messes, with little time spent socializing with and exercising dogs in their care. A better situation for both the staff and the animals would be if the dogs were taken out on a regular schedule to relieve themselves, just like at home. This would allow the dogs time to socialize with the staff and to get some exercise. Human companionship is a major stress reliever for many companion animals. Taking dogs out would make it less stressful for the dogs and would allow the staff to spend more time doing what they enjoy. Taking a fresh look at your whole housing philosophy could be the best way to get the most out of your labor dollar.

CLIENT PERCEPTION

As pets become increasingly important in our lives, we are looking for better care for these valued family members. How you house the animals in your charge contributes greatly to your client's perception of how their animal companions are treated in all aspects of your care. First impressions do matter. It's not unusual for a client to ask why they should board their dog in a concrete box with bars when they sleep on the bed at home. Even if they don't say anything, you can bet they are comparing your housing facilities to how their animals are treated at home.

SURGERY AREAS THAT ARE EFFICIENT AND EFFECTIVE

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TECHNOLOGICAL EXPLOSION

Today we are experiencing an explosion of technological improvements and devices that can enhance your effectiveness, minimize invasive procedures, speed up diagnosis and treatment, increase security, and move you ahead of your competition. Technology as it relates to veterinary hospital design is not just the newest in wiring and equipment, it can also be a whole new approach to the way you practice medicine.

INTEGRATION OF TECHNOLOGY INTO HOSPITAL DESIGN

The one sure thing about technology is that it will change, so wherever possible, provide for flexibility in the construction of your new facility. This could include demountable partitions, raised flooring for cabling, or above the ceiling interstitial space. Some pieces of equipment have particular space and clearance requirements, not only for the final installation space, but also for moving them into place. Oversized doors and hallways can be a helpful addition. There are limits to the practical and economical distances for running telephone and computer cables. Think about supplementary distribution closets in addition to the central computer and telephone room.

Most technical equipment generates heat. It is important to provide cooling for this equipment in the form of chilled domestic water or central air conditioning. Talk to your equipment supplier to determine what your power requirements are, and then increase your feeder and panel size to accommodate both immediate and future power needs.

ELECTRONIC NOMADS

Nomadic computers, such as palm pilots or personal computer tablets, are infrared-based systems and allow continuous and universal wireless capacity throughout the facility. The advantage is the reduced or eliminated need for stationary, fixed computers. Disadvantages include signal interference, dead spots, and difficultly in securing information. Flat-panel, touch-screen nurse call systems are currently being used in human healthcare. These systems speed interaction and communication. Coupled with an infrared locating system, it is possible to keep track of staff, patients, and equipment. It is also possible for a greeter with a wireless headphone to roam the facility and still staff the front greeter desk, because infrared sensors can sense when a client comes through the front door.

AV/IT INTERACTIVE SYSTEMS

Advanced network systems now have the capacity to transmit video camera imaging onto any computer monitor. Video cameras can display live and taped images and monitor patients. Large, flat-screen wall monitors can be located in surgery and public areas for staff teaching or client viewing. Digital x-ray equipment, which allows convenient storing and access of digital x-ray images, is becoming more available. For those not wishing to spend upwards of $40,000, a less expensive approach allows images to be shot onto a reusable plate, and then scanned into a computer. The advantages include greater resolution, instantaneous developing, no messy processing, and the ability to transmit images over the Internet.

ADVANCED IMAGING AND TREATMENT

Oncology is a large emerging field in veterinary medicine. Mobile, time-shared or smaller, in-house MRI and used and reconditioned CT scanners and linear accelerators have made the development of cancer diagnosis and treatment more viable for many practices. There are also companies that will assist with the purchasing, leasing, design, and installation of this type of equipment.

- A CT scanner does not require shielding, but it does require a 16-foot x 18'-foot equipment room, a 6-foot x 10-foot control room, and a 6-foot x 8-foot equipment closet.
- An MRI does not require shielding, but is affected by ferrous metal being located within approximately 16 feet of the facility, including building framework, electrical fixtures and conduit, and passing cars and trucks.
- A linear accelerator requires a clear space of about 20 square feet, with shielding in a maze-type configuration around and over it. Excluding the control room, the required space is approximately 35 feet square and 16 feet high. The shielding can be either concrete, lead and steel, lead-impregnated masonry units, or a combination of these materials. For concrete, the shielding will vary from 3 to 6 feet in thickness, depending on the equipment and surrounding uses. Lead and steel shielding will only be approximately one third as thick, but will cost more than concrete. The linear accelerator suite will require special cooling and clean, uninterrupted power.
- The electrical power requirements for all of these pieces of equipment are significant; be sure to check with your supplier to determine what is required in terms of volts, amps, phase, and duration of need.
- In this day and age, security systems are almost a standard feature in most businesses. They can range from intruder/smoke/fire alarms and battery-powered, push-button door locks to systems that can monitor and track the location of people at any place in a building. While retinal and fingerprint scanners have a ways to go before they are foolproof and affordable, keypads or proximity card readers can be used to access the entry doors of a veterinary hospital.

SUPPLIES

When designing your hospital, remember to include storage space for your treatment equipment, instrument and medical supply needs into the early planning phases. Develop a list of the instruments, equipment and supplies you will need and communicate this to your design and construction team.

The following is a list of potential supplies, equipment and instruments, by room, that might be utilized:

Treatment Room/Pack Prep/lab

- Rolling stool
- Side chair
- Refrigerator for samples
- Walk-on scale
- Wet table (s)
- Waste disposal container (general)
- Waste disposal container (infectious)
- Dental unit—scaler, drill, polisher
- Safety goggles
- Endoscopes
- Doppler
- Portable O_2 unit
- Electrocardiograph
- Test-tube rack
- Blood analyzers
- Centrifuge—blood, urine, hematocrit
- Hemocytometer cell counter
- Unopettes
- Calculator
- Timer
- Ultrasound
- Refractometer
- Glucometer
- Radiography machine and film
- Lead gloves and aprons
- Patient positioning devices
- Radiograph developing supplies
- Gloves
- Masks
- First-aid kit
- Crash cart
- Clippers
- Tonometer
- Ear lavage equipment
- Tongue depressors
- Thermometers
- Splinting equipment
- Culture media
- Diagnostic reagent strips
- Microscope
- Microscope slides, cover slips, and stains
- Bacterial incubator
- Sterility indicators
- Laryngoscopes
- Biopsy jars
- Formalin
- Ethylene glycol test kit
- FeLV/FIV test kits
- Heartworm tests
- Elizabethan collars
- Muzzles
- Autoclave and trays
- Autoclave tape
- Ultrasonic cleaner
- Endotracheal tubes
- Feeding tubes
- Chest tubes
- Stomach tubes
- IV poles and stands
- Fecalizers and flotation solution
- Urine collection containers
- Activated charcoal
- Barium
- Woods lamp
- Surgical pack wraps
- Surgical caps, masks, gowns, and gloves
- Surgical scrub brushes
- Disinfectants
- Surgical-instrument cleaner
- Suture scissors

Surgery

- Surgical blades
- Surgical instruments
- Scrub sink
- Surgical drapes
- Heated surgery table
- Portable suction unit
- Suction hoses and tips
- Crash cart
- Electrocardiograph
- Water-circulating heating pads
- SpO_2 pulse oximeter
- $ETCO_2$ monitor
- Respirometer
- Body temperature monitor
- Blood pressure monitor
- Suture material
- Skin stapler
- Esophageal stethoscopes
- Anesthesia machine
- Anesthesia masks
- Waste gas evacuation
- Infusion pumps
- Induction chamber
- Mayo stand
- Surgical lights
- Lacrimal cannulas
- Cautery unit
- $C0_2$ surgical laser

Hospital Ward

- Nasal oxygen/oxygen cage
- Oxygen flow meter
- Water-circulating heating pads
- Warming blankets
- Towels

- Nebulizer
- Incubator

Pharmacy

- Pill splitters
- Alcohol containers to hold pill splitters
- Pill counting trays
- Pill crusher
- Prescription labels and printer
- Vials and bottles

Clinic Supplies

- Insulin syringes
- Syringes (1, 3, 6, 12, 20, and 60 cc; and 60 cc with catheter tip)
- Needles (25, 22, 20, and 18 gauge)
- Spinal needles
- Jamshidi biopsy needle
- Skin punch biopsy
- Tru-cut biopsy needles
- Sterile water, 500-mL bottles
- Sterile saline for injection
- Sterile saline for irrigation, 6 250-mL bottles
- Urinary catheters
- Butterfly catheters
- Urinalysis tubes
- Jugular catheters
- Bulb syringe
- Blood transfusion kits
- Primary IV sets, secondary IV sets, and extension sets
- IV administration pump
- IV catheters (24, 22, 20, and 18 gauge)
- IV fluids (ie, LRS, Normosol-R, sodium chloride, D5W)
- Male adapter plugs
- Penrose drains
- Porous tape
- Elastic tape
- Hematocrit tubes
- Alcohol wipes
- Bandages
- Gauze
- Stretch gauze
- Chlorhexidine
- Betadine
- Hydrogen peroxide
- Blood collection vials
- Clotting tubes
- Separation tubes
- Lint rollers
- Roll cotton
- Stockinette
- Telfa pads
- Tourniquets
- Splints
- Other
- Cleaning supplies for whole clinic
- Controlled substance safe
- Security system
- Vacuum cleaner

SUMMARY

When designing the surgical procedure areas of your hospital, plan for technology flexibility and changeability. Include your technological, equipment and supply needs into the early planning phases. Develop an understanding of the systems, equipment and supplies you are interested in acquiring, and know the basic terminology so you can effectively communicate your needs and desires to your design and construction team.

MATERIALS, MISTAKES, AND SOLUTIONS FOR YOU

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Selecting materials and finishes for your veterinary hospital is a balancing act. You are balancing a material's color and appearance against installed cost, life-cycle cost, and durability. When looking at appearance, consider what colors, textures, patterns, and sizes are available. When considering cost, identify the initial cost of the product, the cost of installation, the cost of maintenance over time, and the cost of replacing the product at the end of its life cycle. Finally, when examining durability, think about what kind of performance will be required of the product, decide what surface finish will work best, consider the surface over which the product will be applied, look into the cost of maintenance, and check the product life expectancy and warranty. Always attempt to view the product in use, hopefully in an animal hospital, under similar conditions.

The selection of materials and finishes is one of the most important aspects of the design of animal medical facilities. This listing does not attempt to select a "best product" for a certain application nor does it claim to list every product available for every situation. This is simply an abbreviated list of product or finish options that have proven successful over 30 years of hospital design and over 515 successful hospital projects.

FLOORING

Sheet Vinyl

Sheet vinyl is very durable and easy to maintain material. Seams can be heat or chemically welded and the base can be coved for a seamless joint at the base. Select only commercial grade, homogeneous PVC (color and pattern extend completely through the product). Most manufacturers recommend waxing to prevent surface wearing and assist in keeping joints sealed. Rubber base can also be used with this product. Material cost is $3.50 to $5.50 per square foot.

Porcelain and Ceramic Tile

Porcelain and ceramic tile are very durable and beautiful materials for the "front" of the hospital (they can be used throughout if desired). Select only tile with a light traction surface. Use only epoxy grout in medium to dark colors. Rubber base can also be used with this product. Material cost is $4.00 to $11.50 per square foot.

Liquid Applied Epoxy with Ceramic Granules

These floor coatings are very durable and easy to clean, though fairly expensive. Surface preparation is critical and experienced, factory certified, installers are required. We suggest a surface with a light traction surface. Liquid applied epoxy comes in many colors. This product can be coved up wall surfaces. Caution: this is not epoxy floor paint or coating. Installed cost is $6.50 to $8.75 per square foot.

Exposed Concrete Slab

Exposed concrete slabs are normally used in runs and utility areas and are very durable and affordable. Concrete is porous and must be sealed. We suggest a hardener sealer that bonds with the surface. These sealers must be reapplied over time. Concrete floors can be colored integrally or surface stained. Sealer cost is $.50 per square foot more than basic slab. Integrally colored concrete is $1.75 per square foot more than basic slab. Surface stained concrete is $2.50 per square foot more than basic slab.

WALLS

Painted Gypsum Board

Washable eggshell latex enamel can be used in areas of the hospital where mild washing might be necessary. Eggshell alkyd (oil) enamel should be used in areas where a higher durability finish is required. Two-part, high-solids, epoxy (not latex) should be used in areas to be scrubbed frequently (surgery, etc.).

Painted Concrete Block

Washable eggshell latex enamel can be used in areas of the hospital where mild washing might be necessary. Eggshell alkyd (oil) enamel should be used in areas where a higher durability finish is required. Two-part, high-solids, epoxy (not latex) should be used in areas to be scrubbed frequently (surgery, etc.).

CEILINGS

Acoustical Ceiling Tile

The ceiling is one of the few areas in an animal hospital where sound can be absorbed. This can best be accomplished by the use of a lay-in acoustical ceiling system. This system consists of sound absorbing ceiling tiles (usually 0.5 inch in thickness) mounted in a suspended, metal grid. The presence of relatively large amounts of moisture within animal facilities requires the use of 2-foot x 2-foot tiles to resist sagging.

Remember, selecting materials and finishes for your veterinary hospital is critical to the overall performance of your hospital building. Your selection affects more than a material's color and appearance. It affects durability and long-term maintenance for the life of your facility.

SELECTING MATERIALS AND FINISHES

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The selection of materials and finishes is one of the most important aspects of the design of animal medical facilities. This listing does not attempt to select a "best product" for a certain application nor does it claim to list every product available for every situation. This is simply an abbreviated list of product or finish options that have proven successful over 30 years of hospital design and over 515 successful hospital projects.

DISCUSSION OF MATERIALS AND FINISHES

1. Tremendous number of finishes and products available
2. Advertising claims vs. actual performance
3. Finish and material comparison
    a. Finish and material durability
        (1) What is the performance required of the material or finish?
        (2) Surface finish vs. homogeneous finish
        (3) Expansion, contraction and flexibility
        (4) Underlayerment (surface over which a finish material is applied)
        (5) Maintenance required and maintenance cost
        (6) Product life expectancy and warranty
    b. Finish and material appearance
        (1) What appearance is desired?
        (2) Colors available
        (3) Textures or patterns available
        (4) Sizes available
        (5) Maintenance required and maintenance cost
    c. Finish and material cost
        (1) Initial material cost
        (2) Installation or application cost
    d. See the material or finish in use (preferably after years of service)
    e. Ensure that the product is installed properly and according to manufacturer's recommendations (very important for warranty)
    f. Establish a maintenance schedule and maintain the product or finish properly

ROOM-BY-ROOM LISTING OF MATERIALS AND FINISHES

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EXTERIOR FINISHES

Wall Materials

- Brick masonry
- Stone masonry
- Wood siding
- Vinyl siding
- Metal siding
- Exterior insulation and finish system (EIFS)
- Pre-engineered metal building panels
- or Combination of some of the above materials

Soffit, Fascia, and Trim

- Wood
- Vinyl
- Exterior insulation and finish system (EIFS)
- Metal
- Pre-engineered metal building systems

Roofing

- Fiberglass composition shingles
- Metal standing seam
- EPDM single ply roof system (ethylene propylene diene monomer)
- Pre-engineered metal roof panels
- Clay tile
- Fire retardant wood shingles

Walks

- Concrete with light broom finish

Drives

- Concrete paving
- Asphalt paving

INTERIOR FINISHES

Entry Floors

- Porcelain tile (traction surface) w/epoxy grout
- Ceramic tile (Traction surface) w/epoxy grout
- Sheet Vinyl (minimum .080 gauge)

Entry Base

- Porcelain tile
- Rubber base
- Ceramic tile
- Cove sheet vinyl base

Entry Walls
- Gypsum board w/painted surface
- Gypsum board w/type II vinyl wall covering

Entry Ceiling
- Lay-in type acoustical ceiling system (5/8" acoustical panels and steel grid)

Waiting Floor
- Porcelain tile (traction surface) w/epoxy grout
- Sheet vinyl (minimum .080 gauge)
- Ceramic tile (traction surface) w/epoxy grout

Waiting Base
- Porcelain tile
- Rubber base
- Ceramic tile
- Cove sheet vinyl base

Waiting Walls
- Gypsum board w/painted surface
- Gypsum board w/type II vinyl wall covering

Waiting Ceiling
- Lay-in type acoustical ceiling system (5/8" acoustical panels and steel grid)

Receptionist Floor
- Sheet vinyl (minimum .080 gauge)
- Carpet

Receptionist Base
- Rubber Base

Receptionist Walls
- Gypsum board w/painted surface
- Gypsum board w/type II vinyl wall covering

Receptionist Ceilings
- Lay-in type acoustical ceiling system (5/8" acoustical panels and steel grid)

Exam Room Floor
- Porcelain tile (traction surface) w/epoxy grout
- Sheet vinyl (minimum .080 gauge)
- Ceramic tile (traction surface) w/epoxy grout

Exam Room Base
- Quarry tile
- Rubber base
- Ceramic tile
- Cove Sheet Vinyl Base

Exam Room Walls
- Gypsum board w/painted surface
- Gypsum board w/type II vinyl wall covering

Exam Room Ceiling
- Lay-in type acoustical ceiling system (5/8" acoustical panels and steel grid)

Pharmacy and Lab Floor
- Sheet vinyl (minimum .080 gauge)
- Carpet

Pharmacy and Lab Base
- Rubber base

Pharmacy and Lab Walls
- Gypsum board w/painted surface

Pharmacy and Lab Ceiling
- Lay-in type acoustical ceiling system (5/8" acoustical panels and steel grid)

Treatment Room Floor
- Sheet vinyl (minimum .080 gauge)

Treatment Room Base
- Rubber base

Treatment Room Walls
- Gypsum board w/painted surface

Treatment Room Ceiling
- Lay-in type acoustical ceiling system (5/8" acoustical panels and steel grid)

Pack/Scrub Floor
- Sheet vinyl (minimum .080 gauge)

Pack/Scrub Base
- Rubber base

Pack/Scrub Walls
- Gypsum board w/painted surface

Pack/Scrub Ceiling
- Lay-in type acoustical ceiling system (5/8" acoustical panels and steel grid)

Surgery Floor
- Sheet vinyl (minimum .080 gauge)

Surgery Base
- Rubber base
- Cove sheet vinyl base

Surgery Walls
- Gypsum board w/epoxy painted surface

Surgery Ceiling
- Gypsum board w/epoxy painted surface
- Lay-in type acoustical ceiling system (5/8" acoustical panels and steel grid)

Radiology Floor
- Sheet vinyl (minimum .080 gauge)

Radiology Base
- Rubber base

Radiology Walls
- Gypsum board w/painted surface

Radiology Ceiling
- Lay-in type acoustical ceiling system (5/8" acoustical panels and steel grid)

Ward/Bathing Floor
- Sheet vinyl (minimum .080 gauge) w/central floor drain

Ward/Bathing Base
- Rubber base

Ward/Bathing Walls
- Concrete block w/epoxy painted surface

Ward/Bathing Ceiling
- Lay-in type acoustical ceiling system (3/4" acoustical panels and aluminum grid) w/6" sound attenuation batts + thermal insulation batts

Run/Isolation Floor
- Finish concrete w/hardener-sealer treatment (clear)
- Finish concrete w/sealer treatment (clear)
- Finish concrete w/integrally stained concrete surface (colored)w/sealer treatment (clear)
- Finish concrete w/surface stained concrete surface (colored)w/sealer treatment (clear)
- Porcelain tile (traction surface) w/epoxy grout
- Ceramic tile (traction surface) w/epoxy grout
- Porcelain tile (traction surface) w/epoxy grout
- Trowel-on floor (Ceramic Carpet #625 by General Polymers, Inc.)

Run Base
- None
- Porcelain tile (w/porcelain tile floor only)
- Ceramic tile (w/ceramic tile floor only)
- Porcelain tile (w/ceramic tile floor only)
- Trowel-on floor (Ceramic Carpet #625 by General Polymers, Inc.)

Run Walls
- Concrete block w/epoxy painted surface (non-Latex)

Run Ceiling
- Lay-in type acoustical ceiling system (3/4" acoustical panels and aluminum grid) w/6" sound attenuation batts + thermal insulation batts
- Lay-in type acoustical ceiling system (5/8" vinyl coated Fiberglass panels and aluminum grid) w/6" sound attenuation batts + thermal Insulation batts

Storage Floor
- Sheet vinyl (minimum .080 gauge)

Storage Base
- Rubber base

Storage Walls
- Gypsum board w/painted surface

Storage Ceiling
- Lay-in type acoustical ceiling system (5/8" acoustical panels and steel grid)

Staff/Lounge Floor
- Sheet vinyl (minimum .080 gauge)

Staff/Lounge Base
- Rubber base

Staff/Lounge Walls
- Gypsum board w/painted surface
- Gypsum board w/type I vinyl wall covering

Staff/Lounge C
- Lay-in type acoustical ceiling system (5/8" acoustical panels and steel grid)

Doctor's/Business Office Floor
- Sheet vinyl (minimum .080 gauge)
- Carpet

Doctor's/Business Office Base
- Rubber base
- Wood base

Doctor's/Business Office Walls
- Gypsum board w/painted surface
- Gypsum board w/type I vinyl wall covering

Doctor's/Business Office Ceiling
- Lay-in type acoustical ceiling system (5/8" acoustical panels and steel grid)

SITE SELECTION: WHAT YOU CAN'T SEE, BUT NEED TO KNOW

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TECHNICAL ANALYSIS: QUALITATIVE FEATURES + QUANTITATIVE CONDITIONS

Qualitative features provide an evaluative list of criteria useful for comparing sites for suitability to your practice needs, and provide a fairly detailed "snapshot" of an individual site. Categories that comprise qualitative features are Size, Image, Location, Zoning, Visibility, Access, Buildability, Amenities.

Quantitative conditions illustrate the restrictive conditions that must be considered on an individual site to allow you to quantify additional costs that may apply to developing that site. Categories that comprise quantitative conditions are: Covenants, Codes & Restrictions (CC&Rs), Easements, Rights-of-Way, Topography, Hydrology, Environmental Assessments, Utilities, Geotechnical Report.

QUALITATIVE FEATURES

Size

Several criteria are important when evaluating a site for size suitability: square footage/acreage, shape/aspect ratio, frontage, and expansion capability.

Image

Image is certainly a subjective criterion, but an important consideration for success. Is the image you desire for your facility consistent with the neighborhood? Is it permitted? Will the surrounding development have a negative impact on that overall image?

Location

Ask yourself the following questions when evaluating a site. Is the site convenient for clients? Are there major physical impediments to prospective clients—an interstate highway or bridge to cross? What about a railroad or rapid transit route to cross? Are there major psychological impediments—an intervening "bad neighborhood"? Is the site on a major street? Can driving directions to the site be easily described?

Zoning

In most states, local municipalities produce what is known as a Zoning Code. This local zoning code will impact your site and its development at several levels. Among those areas restricted by the codes are use, setbacks, parking, loading and trash, screening, landscaping, signage, building height, and lot coverage/site density.

Visibility

It is important that your site provide opportunities for visibility of your building and sign from adjacent thoroughfares. Both daytime and evening visibility should be considered.

Access

The ability to easily enter and exit your parking lot will make life easier on your clients and in turn provide added incentive for them to visit. Check both right and left turn access, curb-cut locations (existing and potential), traffic islands, turn lanes, medians, and other traffic impediments. Visit the site during busy traffic times to see if nearby traffic control devices back traffic up to your selected site, making egress and access difficult at certain times of the day.

Buildability

Look at the overall "lay of the land," checking for extreme slopes or depressions that could make development difficult or more costly. Remember that earthwork is expensive! Even "flat" sites can be difficult when offering no natural drainage for storm water.

Amenities

Existing improvements or natural occurrences can enhance a property value. A previously placed perimeter fence can defer that expense for you. Mature landscaping used wisely can provide a finished landscape immediately upon building completion. Perhaps the property borders on a park system with access to public features like bike paths, designating walking areas, and playgrounds. This can also enhance a project value.

QUANTITATIVE CONDITIONS

Covenants, Codes & Restrictions

A property may have development restrictions and design guidelines known as CC&Rs. These guidelines are typically more stringent than municipal regulations and are often associated with commercial development communities. These design guidelines can range from allowable uses and lot coverage to acceptable building styles.

Easements

Public and private accesses to a property are often legally granted which inhibit construction improvements in designated areas. Easements can be at, under, or above ground level. The more typical include driveway easements (at grade), pipeline or wire way easements (underground), and power line easements (above ground). Surveyors can research if any easements exist on a specific property.

Rights-of-Way

The municipality governing the street on which a property is located will enforce a distance from either side of the street centerline for road improvements, utilities, sidewalks, etc. This can extend onto your property where improvements will be prohibited. These rights-of-way have been known to extend 20 to 50 feet onto a property. Be sure to research current rights-of-way as well as the possibility for future extensions.

Topography

A topographic survey maps the contours of the ground. Topography affects drainage of surface runoff, slopes of drives, parking lots, sidewalks, and finish floor elevations. Altering severe topography is expensive! Surveyors prepare a topographical survey.

Hydrology

Directly related to topography, municipalities have exacting restrictions in how to manage storm runoff. All storm water that falls onto your site must usually be retained on site until natural evaporation/percolation, or detained in a holding tank (or pond) equipped with a controlled release. Civil Engineers will be required to calculate and design hydrology requirements.

Environmental Assessment

Any evidence of environmental contamination is normally addressed in a Phase One Assessment. Should this physical and historical research indicate an environmental contamination possibility, a Phase Two study must be commissioned to determine presence and levels of contamination.

Utilities

The availability of service utilities for connection is the first assessment to be determined. Domestic water, sanitary sewer, electricity and telephone services are the most critical. Natural gas, storm sewer, fire protection, and high-speed internet are highly desirable. Available service size must be documented for suitability and the availability and cost of connection (impact fees) must be calculated.

Geotechnical Investigation

The suitability of soil conditions on a site must be assessed for several needs. Foundation types, paving types, drainage and allowable excavations will all be dictated by the findings of the geotechnical report. This is typically accomplished through soils borings that are analyzed in a laboratory and written by a certified engineer. Poor soil conditions can create costly construction remedies!

SUMMARY

Site selection is the initial major decision in any building project. This decision can either dramatically enhance your prospect to succeed or keep your practice from reaching its full potential.

Initially, consider obtaining a consultant to perform a demographic/market analysis to evaluate the present and future market conditions. Many veterinary specialist consultants have entered the market and provide a more in-depth understanding of the profession and its unique needs.

Second, gather the information necessary to conduct a technical analysis. If you become overwhelmed or simply prefer to obtain a consultant to complete this for you, the service is available.

In any event, do the research necessary to make the best decision.

EFFICIENT AND FUNCTIONAL FLOOR PLAN CRITERIA

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PLAN FIRST

Before the initiation of a floor plan design, your design professional will complete what is known as a Program. He or she will utilize your input (and possibly your staff's) to determine your project goals and objectives. This information may be gathered through interviews and/or questionnaires and if applicable, through their own, personal experience of this building type. Answer the following questions in preparation to begin.

Define Your Practice

- Small Animal? Large Animal? Exotic?
- Emergency care? After hours or 24-hour?
- Specialty/Referral?
- Boarding? On occasion, within hospital wards? Separate wing?
- Full service "pet resort"?

Outline Medical Services to be Offered

- Diagnostic radiology? Treatment radiology?
- Other specialty services?
- Animal behavior?
- Rehabilitation?
- Client education seminars?

Outline Ancillary Services to be Offered

- Retail? Small alcove in lobby, "boutique" or full service?
- Daycare and/or training?
- Adoption? Animal wellness?
- Grooming? Clinical staff or outside contractor?
- Standard kennel and cage boarding? Luxury suite and feline condo boarding?

Plan for the Future

- What level of growth would you prefer?
- What additional client services might be offered?
- What is your exit strategy?

When complete, the Program, as a document, will identify a series of rooms and/or spaces that are necessary to meet those goals and objectives. Square footage calculations will be assigned for each room and/or space, and the various relationships of those rooms and/or spaces will begin to develop.

Once the programming is complete, conceptual design can begin. Veterinary facilities in general can be divided into three zones—the public zone, the clinical zone, and the animal housing zone.

- **Public Zone**: Main Entry, Lobby (waiting area), Reception, Exam Rooms
- **Clinical Zone**: Pharmacy, Lab, Treatment, I.C.U./Recovery, Radiology, Surgery, Pack/Prep./Scrub, Offices, Isolation (optional), Staff Lounge (optional)
- **Animal Housing**: Cage Wards, Run Wards, Utility, Laundry, Food Prep., Bathe, Isolation (optional), Staff Lounge (optional)

There are many spaces that your program may require that are additional to those illustrated in the example provided above. Their location is established in part by your programmatic requests, but also by other determining factors such as function, circulation, hierarchy, and in some instances buildable perimeters.

DESIGN SECOND – A FEW EXAMPLES

Specialty/Referral Hospital

The design of the *public zone* can take on different configurations based on programmatic requests and the manner in which a group may choose to practice medicine. Some referral facilities have requested to incorporate separate public zones specific to certain specialties, which then share the clinical and animal housing zones. In this instance, one might consider to develop a floor plan that identifies a number of separate wings (public) that attach to a larger central mass (clinical and animal housing). Each individual wing would house the public areas such as the *main entry, waiting, reception, offices and exam rooms,* and have direct access into the central clinical and animal housing zones such as *pharmacy, lab, special procedures, treatment, wards, laundry, etc.*

Other referral facilities have requested that all of their exam rooms be located adjacent to one another with a large lobby and reception feeding into them. In this instance, the exam rooms would be grouped by specialty and located directly adjacent to their neighboring special procedures room. This controls the circulation pattern of the specialties and allows the specialists and their staff to work more efficiently.

Small Animal Hospital with Boarding Services

Again, based on the requests presented in the programming document, this type of facility could take on a number of configurations. It is important to understand the components identified and the relationships between them.

Is there a desire to market the boarding component by locating it adjacent (and visible) to the public zone? Is this a component that will house luxury boarding suites and feline condos—a space that deserves recognition by your clinical clients? Or is this truly a "secondary" component with no need to market; a grouping of standard runs used primarily during peak seasons such as the winter holiday? This type of boarding component is typically located in the animal housing zone—furthest away from the public zone—because the runs are often used as overflow for the hospital.

SUMMARY

A functional floor plan is the single most important element in your project. Creating *your* great floor plan is up to you and your design professional. While many of the functional relationships do remain the same for any well-designed veterinary hospital, it is important to determine and incorporate what works best for you and your practice.

There is a design system, which is taught in the architectural profession. Just as a veterinarian must prepare for a specific surgery, an architect must prepare for a specific building. A great building design—one that is functional, efficient, aesthetic, stout and budget conscious—is one that is planned first and designed second.

LIGHTING AND COLOR IN VETERINARY FACILITY DESIGN

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LIGHT

Natural vs. Artificial

Natural light can be categorized into daylight or sunlight, candlelight and firelight. As one may notice, natural light is always in motion. Daylight, for example, is constantly changing. As the day progresses, and the seasons change, variations of tone, intensity and color become apparent. Consider the following properties when incorporating natural daylight.

- Northern light has a cold, greenish cast
- Southern light has a warm, pink cast
- Eastern light has a harsh, yellow cast
- Western light has a red-orange cast

Artificial light is not a true substitute for natural light, but with the current systems and fixtures available, it is possible to manipulate light to provide a desired contrast and variety. Different bulbs create varying qualities of light that have a direct effect on how a space is perceived. Consider the following properties when incorporating artificial light.

- Fluorescent light has a cold, blue cast
- Tungsten light has a slight, yellow cast
- Halogen light has a bluish cast
- Incandescent light has a warm, yellow-orange cast

Illumination: Quantity and Quality

Illumination is more recognizably defined as both the measurement and character of light. Light measurement is based on output, level, and brightness. Light output (lumens) is the most common measure of light and is labeled on all light sources. Light level (illuminance) is the light intensity measured on a plane at a specific location. Brightness (luminance) is the measurement of light which travels away from a surface in a particular direction.

Glare, uniformity of illuminance, and color rendition define the character (quality) of light. Glare is the effect caused by luminances in the visual field that are too bright. The relationship between the luminance of an object and its background is called contrast. A bright object alone may not cause glare, but if that same bright object is located within a dark background, it usually will. For example, a visual task may become easier with increased contrast, but too much contrast may cause glare, making the visual task more difficult. Associated problems are discomfort, annoyance, and reduced productivity.

Uniformity of illuminance considers the even spread of light over a specific area. If distribution is off, associated problems such as inadequate light levels, the visual discomfort or of bright spots, and patches of light may become apparent.

Color rendition is the color appearance of an object or space when it is lighted. Light sources vary in their ability to accurately reflect the true colors of people and objects. They can significantly impact our perceptions of a space by altering its character. Be cautious of this when working with color. It is difficult to anticipate the effect of coordinated and complementary colors upon installation. Select your desired finishes and color schemes under the exact or similar lighting conditions with which they will be seen when your project is complete.

Light Bulbs and Light Fixtures

Known as lamps and luminaires in the lighting industry, a light bulb (lamp) is the primary source of light, while the light fixture (luminaire) uses reflectors and lenses to help spread out and focus the light where it is needed.

Light Bulbs (lamps)

- Fluorescent bulbs have a long life span, use a low amount of energy, and are perfect for shadowless, general lighting.
- Tungsten bulbs are your ordinary household light bulbs.
- Halogen bulbs are energy-saving and emit what is known as "white light" — a pristine quality of light that has minimal effect on color.
- Incandescent bulbs have a short life span, but emit a quality of light that is warm and aesthetically pleasing.

Light Fixtures (Luminaires)

- Overhead fixtures are large, ceiling mounted fixtures that provide general background light and **can** create an illusion of greater space.
- Pendant fixtures hang from the ceiling and splash light toward the floor, ceiling or both. They are used for "atmosphere" and/or general light.
- Downlight fixtures are small and unobtrusive; can be surfaced mounted to the ceiling or recessed within. They provide general, mood, or task light.
- Uplight fixtures are designed to bounce light off of ceilings or walls, scattering in such a way that shadow and glare are absent.
- Track lighting is a system that combines more than one component. Small light fixtures are attached to a rail or pair of cables that provide the electrical current and allow the fixtures to reposition and rotate as necessary to focus light onto a specific surface or object. They can be mounted to the ceiling or wall, and are used for accent light

COLOR

Color makes an immediate and lasting impression, and when executed well, can be the success of any project. Developing the ability to properly apply color begins with studying the basic principals of color theory.

Three Dimensions of Color

Hue is another name for color. There are 12 hues, for example, in the color wheel.

Value is the lightness or darkness of a color that indicates the quantity of light reflected. It is the relative lightness or darkness of a color that is determined by the amount of black or white present in a color. A "tint" is created when white is added to lighten a color. This gives a color a high value. A "shade" is created when black is added to darken a color. This gives a color a low value.

Intensity is the saturation or strength of a color determined by the quality of light reflected from it. It is determined by the amount of gray added to a color. For example, the "pure" color of red will have a strong intensity while a muted color of red, one which has a great deal of gray added, will have a low intensity.

The Color Wheel

Hues (colors) are defined and organized by the color wheel, which is made up of twelve colors, each at their full intensity, and arranged in accordance with the visible light spectrum. Primary colors – red, yellow, blue - are the source from which all of the other colors are derived. Secondary colors – orange, green, violet – are the combination of two primary colors. Tertiary colors – red/orange, orange/yellow, yellow/green, green/blue, blue/violet, violet/red – are the combination of two secondary colors.

Color Relationships

Analogous colors are three to five consecutive colors on the color wheel. Because these colors have the shortest interval between them (directly adjacent to one another), they have the most harmonious relationship. An example is the combination of red, red/orange, orange, yellow/orange, yellow. If unfamiliar with color, harmonious color schemes are the easiest to design.

Complementary colors are the opposing colors on the color wheel. Because they are opposites (furthest distance from one another), they have the highest contrast and greatest intensity. Some examples are red with green, blue with orange, yellow with purple. When incorporated successfully, these color schemes make a significant statement, but they are the most difficult to design.

Neutral colors are created by mixing equal amounts of two complementary colors. They are necessary to balance, dilute, or set-off bright colors, and are the perfect backdrop for artwork display. Examples of neutral colors are gray, beige, tan and taupe.

Color Families

Colors are often said to be warm or cool in temperature and thus all colors are classified in one of two families. Warm colors are associated with sun and fire, while cool colors are associated with air, sky and water. When referencing the color wheel, warm colors are those located adjacent to red, orange, and yellow. Cool colors are those located adjacent to green, blue, and violet. Something to note, however; there can be cool shades of red, and warm shades of blue. It is determined by the mixtures of hues in either color, or the quality of warmth and coolness in a color that is altered by its neighboring hues. In other words, be certain to hold two colors of green next to each other before assuming the two will match. When this is done, it becomes much easier to see which reflects yellow and which reflects blue. Green will appear warm with the addition of yellow, or will appear cool with the addition of blue.

Color Psychology

Color communicates emotion, creates mood, and affects our energy. It has an emotional impact that can delight you or distress you, and may evoke both pleasant and unpleasant emotions.

Red

- Brave and bold, brings heat, intensity and passion
- Can increase the heart rate, raise blood pressure, and cause rapid breathing

Orange

- Contains the excitement implied by red, the cheerfulness associated with yellow
- Considered as a "happy" color

Yellow

- Stimulating and promotes activity, raises the spirit and brings a sense of joy
- Prolonged exposure to intense yellow can cause anxiety

Green

- Signifies life, freshness and harmony, and has associations with health and well being
- Commonly used in restful spaces

Blue

- Considered magical, encourages thought and contemplation, and has associations with simplicity, purity and truth.
- Known to lower body temperature, pulse rate, and blood pressure
- Can have a depressive effect if overused

Violet

- Carries the contrast of liveliness and calmness, therefore has associations with tension and ambiguity
- Light shades are viewed as sensitive and artistic, and are associated with spirituality
- Deeper shades are thought of as dignified, and are associated with royalty

White

- Associations with purity, cleanliness, simplicity and clarity.
- When used alone, may suggest emptiness, blankness and boredom
- Symbol of modernism

Black

- Represents strength, seriousness and formality
- Contains lack of hope and therefore depresses; has negative associations of emptiness and death
- Used in moderation, implies a level of sophistication

APPLICATION

Light and color are two of the major components in transforming any space. A single room has the ability to reflect different spatial impressions simply by changing the location or type of light source, or by adding a different color.

Light

- A high level of illuminance in a room can give the impression of a larger volume.
- To raise a ceiling visually, splash a heavy concentration of light toward the ceiling or upper portions of the walls.
- If a ceiling is too high, incorporate luminaires (light fixtures) that allow no light out of the top. A shadowed ceiling will appear lower.
- "Open" a small, confined room by washing a wall with light.
- If a room is too wide, illuminate its narrow walls.
- If a room is too narrow, illuminate its wide walls.

Color

- Warm colors advance; appear to draw surfaces closer.
- Cool colors recede; tend to make a small space look larger.
- Dark colors absorb light, and create the appearance of an intimate space.
- A light color on the floor will make a room grow.
- A dark color on the floor will make the room appear smaller.
- A long, narrow room will seem more in proportion if its far wall is a dark color and its side walls are a light color.
- A low ceiling can be painted white to visually raise its height.
- Add colors associated with red, orange and yellow to rooms that face north or east, or those that receive no natural light. This will add warmth and energy.
- Add colors associated with green, blue and violet to rooms that face south or west, or anywhere there is a great deal of natural light. This will cool the room and add a calming atmosphere.

DETAILS THAT MAKE THE DIFFERENCE: TEN SUGGESTIONS FOR RECEPTION AND EXAM ROOMS

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Clients today, have high expectations and take their business where their expectations are met. If your business reflects the highest of quality, so should your building. With respect to image, nothing influences a client more than the "front end" of your facility—the space or combination of spaces defined by architecture, light, color, furniture, signage, organization, and function. The interrelationship of the waiting, reception, and exam rooms, how they are managed and how they are maintained, are most likely a direct reflection of your practice in the eyes of your clients.

Without considering the exterior, first impressions are established the moment your client enters the building. Consider what it important. For example, your reception area is provided to control the function and organization of both your clients and your business. However, "less really is more." It is not necessary to expose the mechanics for your administrative requirement. What is important is organization and efficiency.

The way in which your exam rooms relate to waiting and reception is a critical design element. Their organization within the front end should consider functionality, efficiency and often times, privacy for both your clients and staff.

The following suggestions offer ideas for you to consider in planning a new facility or remodeling an existing practice. Speaking from experience, I know that incorporating only a few will begin to lead you down the path to a successful "front end" design.

SUGGESTION 1

Organize circulation to make it easy for your clients/patients/staff

- Locate the receptionist/greeter within direct eye contact from the client upon entry into the facility.
- Present a visible reception desk and an obvious path of travel clear of waiting clients/patients.
- Provide ample clearance for clients/patients to enter facility and wait momentarily for the receptionist/greeter.
- Identify separate check-in and check-out stations at reception even if this is incorporated within a single desk.
- Locate retail items within easy access from check-out at reception.
- Provide an obvious path of travel from the exam rooms to the check-out station at reception.
- The concentration of client seating within the lobby should be pulled away from main flow of client/patient traffic.
- Do not dictate separation of species in the lobby. Provide options to allow your clients the decision based on comfort.
- Locate a behind-the-scenes administration area central to reception and the exam rooms.
- Provide a private exit when and if necessary for the comfort of a client.
- Monitor client/patient traffic with visual cues.

SUGGESTION 2

Add an element of surprise

- Design for a "feature wall."
- Incorporate interior architecture.
- Apply an accent color to one wall.
- Spend a little more on a fancy finish material.
- Feature a piece of artwork or graphic mural.
- Open an area with glass to provide a glimpse into the functioning hospital beyond.
- Include a water feature or possibly a fireplace—whatever may be in context with your community.
- Design around an atrium, central courtyard.

SUGGESTION 3

Break the monotony

- Consider a lighting design that incorporates different light fixtures and varying light levels.
- Expose architectural features on the interior.
- Add volume and depth to an otherwise boring ceiling by varying its heights and finishes.
- Educate and entertain your clients by enticing them to wander about the lobby to visit/experience different areas—retail center, feline boarding, educational alcove, hospitality bar, a viewing window into a physical therapy room, puppy daycare or agility training yard.

SUGGESTION 4

Accentuate with color and light

- Add visual depth from one space to another by pulling specific walls forward with color.
- Identify circulation paths with different colors.
- Provide a little atmosphere with ambient and accent lighting.
- Raise an otherwise low ceiling by flooding it with light.
- Incorporate a large graphic paint pattern as an alternative to framed artwork.

SUGGESTION 5

Keep it clean and simple

- Eliminate the clutter.
- Conceal wiring wherever possible.
- Consider built-ins vs. mix-and-match.
- Organization is key.
- Personal style(s) to remain at home.
- Keep wall display(s) to a minimum

SUGGESTION 6

Incorporate finishes that are easy to maintain and will prove successful over time

- Porcelain floor tile
- Tile wall base
- Epoxy grout
- Vinyl wall covering
- Ceramic wall tile
- Corner guards
- Stain resistant paint
- Solid surface
- Plastic laminate
- PVC edgebanding

SUGGESTION 7

Borrow natural light

- Incorporate interior windows to transfer natural light from one space into another.
- Design for skylights or light tubes to splash interior rooms with natural light.
- Incorporate reflective materials sparingly, but to pull the appearance of natural light into darker areas, areas without windows.

SUGGESTION 8

Design with efficiency in mind

- Understand that the new facility (due to its increased size) will require a new procedures, and additional staff. "We do it this way now" is not always a valid reason.
- Space adjacencies should be planned to achieve the shortest path traveled.
- Make the most of your computer system/hardware.
- Everyone/everything has its place.

SUGGESTION 9

Make it user friendly and ergonomically ideal

- Install lift tables and rolling gurneys in exam rooms.
- Raise counter heights to accommodate for standing workstations.
- Provide a low 30" high workstation in consultation and/or euthanasia exam rooms to allow the flexibility of speaking with a client/family in a seated position.
- Incorporate larger exam rooms for additional clearances and more "elbow room."
- Install wall-mounted flat screen monitors on rotating arms or provide two monitors in each exam room.

SUGGESTION 10

Keep it comfortable

- Incorporate different types of seating and furniture to accommodate all ages of clients.
- Design light levels and incorporate light fixtures based on function of space.
- Consider the psychological effects of color.
- Keep room temperatures under control with adequate heating and cooling.
- Maintain proper ventilation to keep rooms free of odor.
- Block unnecessary noise transfer from one space to another with proper room construction.
- Have the ability to offer client/patient privacy when necessary.
- Whenever possible, provide natural light.
- Include ergonomic equipment and design custom workstations

CLUES FROM KATRINA: HUMAN–ANIMAL BOND AND DIVERSITY IN PRACTICE

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Much has been written about the human–animal bond and the benefits of the bond to humans in the relationship. Certainly there is no question about the health benefits; studies show animal owners tend to have reduced stress levels, lower cholesterol and blood pressure, and improved mental health status. Several papers, most notably, by Drs. Sue Ellen Brown and Ronnie Elmore, have been written measuring the quality of the bond between people and the animals they own. These papers characterize pet owners as having higher or lower pet attachments based on race, ethnicity, and/or cultural norms. Brown's paper in particular demonstrated the difference in pet attachment among White and African American individuals. What these papers and much of the research in the human–animal bond area neglect to do is explore the bond in a manner that considers the impact of multiple dimensions of diversity including culture, economics, and historical context and how the bond is outwardly manifested under these influences. This article seeks to explore some of these elements and their impact on the outward manifestation of the human–animal bond. Hurricane Katrina's aftermath in New Orleans presents an interesting case study with which to consider this issue.

The presumed standards by which pet attachment is measured are numerous. Are the animals named, even with used in a utilitarian manner? Do owners *love* their animal? Do they provide regular and routine veterinary care for their animal? Is the animal allowed inside the house, inside the bedroom, on top of the bed? Is the animal spayed or neutered? Are there visits to the park, clothing and accessories, traveling on trips? Are owners considered owners and/or guardians? These questions are often considered when looking at pet attachment. The questions are often also used when assessing populations that are expected to be fairly homogenous. There is an expectation that there is consensus on how pet attachment and ownership are both defined. However, when we look at specific populations in this country, such as groups historically marginalized by race, ethnicity and class, for example, these oft accepted benchmarks may lead us to assert that some pet owners are not attached or are even unable to attach to their animals. No, regular veterinary care is not provided. No, the animal is not allowed in the house. No, the animal is not sterilized. Elmore asserts that the barriers to higher levels of pet attachment may also bear responsibility in maintaining the racial and ethnic homogeneity with within the veterinary profession. While in the theoretical sense we know that attachment can exist in these instances, in the practical sense, policy and practice in and around the veterinary profession is driven by the responses to these types of questions about the bond.

HURRICANE KATRINA

With a population just shy of 500,000 prior to Hurricane Katrina, New Orleans was known as a bustling tourist attraction with its French Quarter, Mardi Gras celebrations, and jazz clubs. Just beyond Bourbon Street, however, just over a quarter of the city's total population lived below poverty level. The median household income was just over $27,000 a year. Eight percent of residents were unemployed. African Americans comprised 68% of the city's population, although it is important to note that New Orleans people and culture are strongly knit to countries around the word including France and Spain as well as numerous Caribbean and African countries.

According to the New Orleans SPCA, the city had one of the largest stray animal populations in the country prior to the hurricane. Most animals were not sterilized. Interviews with SPCA staff asserted that many New Orleans residents owned pets, although the number is unclear. However, it is important to note that ownership often carried different definitions including multiple owners and transient neighborhood ownership. Few pets were sterilized and frequently did not receive preventive care for ailments such as heartworms.

After the storm, much of the city's dominant population evacuated to other cities around the country. The total population of New Orleans declined by approximately 40%. The number of families making less than $15,000 per year declined by more than half after Hurricane Katrina. The remaining residents of New Orleans tended to be far more affluent than the evacuees. They also were more likely to be white.

An estimated 15,000 animals were rescued after the Hurricane Katrina in New Orleans. Nearly 95% of the animals were intact, and nearly as many tested positive for heartworms. Many animals had conditions that were diagnosed as preexisting and chronic illnesses. Efforts to reunite pets with owners were a priority and many animal shelters created digital registries to identify the animals and the owners who surrendered them in hopes of facilitating future reunions. Shelter facilities for animals and New Orleans were severely limited making the need for animals to be transported across the country to accommodating shelters a necessity. Unfortunately, this also raised the risk that many reunions between owners and their pets would not occur. Many animals that could be fostered in the interim were, while others were formally adopted immediately. The LA-SPCA estimates that 15% to 20% of animals recovered were reunited with their owners in the first year after the storm.

In the aftermath of Hurricane Katrina, various news outlets began covering stories on New Orleans residents who stayed behind to weather the storm with their pets. Coverage included stories of abandoned animals and broken hearted owners. Of course, one of the most iconic images of the human–animal bond is the inconsolable child boarding the bus as he is separated from his pet dog, Snowball. Stories also included happy reunions of pets and owners. While much of the post-storm analysis critiqued the response to the city's human suffering through the lenses of race and class, little of this analysis was directly applied to the characterization of the response with respect to pet ownership, pet care and the human–animal bond.

ATTACHMENT CASES

More than two years after the storm, much of New Orleans' population remains displaced and so do their pets. The impacts of culture and class demographics are seen clearly in the aftermath of the storm. Many families were unable to evacuate because of limited resources and access to transportation. Evacuation plans did not take pet/animal evacuation or financial status into account. Still more who may have considered evacuating did not because of the limited ability to carry pets with them. More affluent residents could seek shelter out of town in hotels that welcomed pets. Far more evacuees sought refuge in shelters that did not allow pets.

As recently as the spring of 2007, cases to determine ownership were still winding through the court systems. In Phoenix, a couple that adopted a Katrina dog declined to return the dog to his previous owner. The couple reasoned that the animal would be better suited with them because the previous owner is on a fixed income. The Christian Science Monitor reported that this defense was common among defendants as they "claim that the animals are better off in wealthier homes than in poorer ones, where care may be substandard." The article went on to assert than rescued animals were essentially moving "from poor to rich and from black to white."

Economic status and cultural norms may result in varied standards of pet care; however, these differences do not necessarily reflect the true level of attachment between the owner and the animal. Much like human health, the challenge for veterinarians is to embrace practices that are able to facilitate the bond in a manner that respects cultural perspective and economic limitations. In human health this concept is called cultural competence. While there are numerous definitions for this concept, for these purposes, cultural competence will be defined as a set of values and principles, and demonstrable behaviors, attitudes, policies and structures that enable professionals to work effectively cross-culturally.

CULTURAL COMPETENCE

The profession does not do a very good job of educating veterinarians about how to treat the client. Colleges of veterinary medicine now include communication coursework to facilitate positive interactions with the client; however, these courses tend to be brief and not comprehensively built into the curriculum. Based on human medical models, we understand various patterns of behavior with respect to health care among people of color and poor people in this country. Compared to their white and/or more affluent counterparts, these individuals are less likely to seek regular medical care, less likely to practice male sterilization, and less likely to donate organs. They are also more likely to have a lower life expectancy and more likely to have a higher level of distrust of the medical establishment, thanks in part to medical legacies like the Tuskegee Syphilis Experiment.

While veterinarians are among the most trusted professionals in the country, it cannot be assumed that these particular populations are not influenced by these realities in their relationships with all health professionals including veterinarians. These experiences overlay a very individualized sense of the relationship between the owner and the animal. Practicing veterinarians must consider the various influences of culture and economics in a meaningful way that will engender enhanced trust with the special populations they may engage. The bond may not always look the same, and it is critical that individuals are not penalized or stereotyped because the way the human–animal bond is outwardly manifested.

There are a variety of concrete ways to create a practice environment that reinforces a positive human animal bond among special populations. Veterinarians and their staffs will benefit from basic diversity training programs as well as enhanced communication training that addresses important issues such as cross-cultural communication and nonverbal communication. A diversity audit of the practice is also important in identifying areas for improvement for veterinarians and practice managers to address in the core business model of the practice setting. The audit can evaluate whether a practice considers the needs of diverse populations by evaluating the physical environment, materials and resources, communications styles, and practice values and attitudes. Some key elements that must be reinforced in the audits include that limited English proficiency is not a reflection of intellect, financial restrictions that impact the course of treatment are not a reflection on the level of pet attachment, and culture has a strong influence on the value and meaning of medical treatment for both humans and animals. Model audits from human medicine, such as those used by the American Association of Family Practitioners, may be adapted for use in the veterinary clinic setting.

In conclusion, as we look at pet attachment and the tenets of the veterinarian's oath, the profession must consider the relationship between the veterinary profession and the clients who are served. The dimensions of pet ownership and the human–animal bond are more fluid across culture and class than we care to admit. In our denial, we may be perpetuating what we are trying to create, a public that has a strong pet attachment that is able and empowered to provide adequate medical care for their animals.

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THE ECONOMIC REALITIES OF DIVERSITY

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As a matter of course, diversity efforts are usually attributed to a moral principle about equity. Historically marginalized populations seek equity in various areas including education, the workforce, and access to basic healthcare. Diversity efforts still seek to equalize populations; however, an increasing number of individuals and, more globally, companies embrace diversity efforts as a matter of both practicality and increased competition. Large companies have implemented numerous recruiting and marketing strategies to tap markets within underrepresented and/or marginalized communities with the recognition that the opportunity to meet specialized needs creates a competitive advantage. This article seeks to provide a broad perspective of the economic impacts of diversity in veterinary medicine.

The National Commission on Veterinary Economic Issues conducts studies with the goal of creating a more productive veterinary business. The Commission's studies have encouraged owners to alter business practices to improve service delivery, practice management, salary and other elements within the scope of veterinary practice. To date, however, NCVEI has not taken a serious look at how diversity impacts veterinary businesses, with the noted exception of three studies specifically focusing on gender and/or generational issues. Despite NCVEI's lack of interest in this area, a body of research devoted to diversity's overall impact on business has been growing for more than 30 years. In the last 10 years, an increased emphasis has been placed on directly tying the economic realities to the pursuit of diversity in business. Admittedly, the active pursuit of diversity in business has naysayers that cite a lack of applicants, difficulty in managing diverse working groups, and length of time for economic payoff as critical reasons for allowing the business sector to remain homogenous. But much of the business sector has accepted diversity as something to be pursed because of the tangible advantages it produces for a business.

It is time for the veterinary profession to join this discussion and begin to answer key questions about this issue that directly impact all sectors of the profession, but certainly most acutely those professionals in clinical practice. Is there a need to do a diversity audit in veterinary practices? What is the impact of doing such an audit? Are diverse staffs more embedded in the practice, producing a reduction in staff turnover? Are clients' linguistic needs met in current practice structures? Are veterinarians certain they are receiving informed consent to do a procedure from a client whose English skills are limited? How do elements of culture and class impact service delivery in the practice setting? These questions are constantly asked in the human medical establishment, not just because they impact the quality of care delivered to the client which is the highest priority, but because they also impact the bottom line of a practice and or hospital. As the profession begins to explore the economic impact of diversity in the profession, three areas of study are key: workforce diversity, understanding the changing markets locally, nationally and globally, and long-term commitment to diversity initiatives.

WORKFORCE

The veterinary profession is not terribly diverse racially. According the US Census Bureau, the profession in 2000 remained over 92% white. In fact not much has changed over the years, when looking at student enrollment data provided by the Association of American Veterinary Medical Colleges (AAVMC). In the last 10 years, non-white student enrollment has grown only 2.5%.

In 2007, the Journal of American Veterinary Medical Association included an article that celebrated presence parity of women in the profession. However, data also collected the by the AAVMC shows that women now comprise nearly 80% of all enrolled students. The number of men pursing careers in veterinary medicine has been on a decline for more than 30 years. In short the profession is changing, but its change is primarily moving from a profession of white men to one of white women.

While all of the groups that are presently in the profession and those who will come in the future will certainly contribute to the advancement of the profession, the lack of diversity creates a missed opportunity to maximize opportunities in the profession in the coming years. A diverse workforce has been shown to have a positive relationship with financial performance and specifically with the increase in net income of managers. Numerous studies have suggested that diverse workforces, which would typically be defined as having a greater than 10% non-white population, have enhanced capacity for problem solving, creative ideas and productivity. The workforce component is not just based on representative diversity, but also how that workforce is managed. Managers of more diverse workforces are tasked with creating a workgroup that really maximizes the position and the potential of the business. Admittedly this can be a difficult and costly task. It is certainly difficult to manage of group of people of different backgrounds and perspectives, particularly if they are not like minded. Such systems can have costs, including friction among staff and staff turnover, which are clearly able to be financially quantified for a business. However, management of a diverse workforce requires a skill set worthy of investment. A recent study of US companies found that in those surveyed, "diversity was leveraged by using employees of all backgrounds to increase innovation (61% of respondents); by using diverse employees to recruit new workers (59%); by integrating diversity into the business strategy (53%); by meeting the unique needs of customers (53%); and by using diverse experience on projects (52%)."

In planning for the future, there must be an increased interest and commitment to creating diverse profession. There is an inherent difficulty in recruiting a diverse workforce in a profession that is racially over 90% white with an academic system that is educating primarily women. The solution to this dilemma is twofold. On an individual business level, "the issue is not whether there are enough diversity candidates to go around to every organization. The issue is whether you can attract and recruit enough for your organization. This is called competing for resources." In a more holistic sense, diversity has to be considered a long-term commitment that includes nurturing interest in the profession and providing opportunities to explore the veterinary profession. Underrepresented students, which now include male students, need increased exposure to the profession and volunteer opportunities to work in a variety of practice settings. This does require that practices invest time, space, in some cases financial compensation among other resources; however, these interested students potentially become walking advertisements for your business. They may also be easier to recruit to your business upon the completion of their studies.

DEMOGRAPHIC AND MARKET CHANGES

Like other businesses, the veterinary profession must understand the dynamic changes in the various markets in which the profession is engaged. Population changes in this country and around the world are happening very quickly. Between the 2000 Census and the 2005 Community Survey, the White population in this country declined by nearly ½ percent. Hispanic and Asian populations are expected to continue being the fastest growing ethnic and racial groups in the first half of this century. In addition, the number of bi- and multi-racial individuals in the country in on the rise. This group currently makes up more than 2% of the overall population.

While many states are still fairly homogenous with respect to race, projected population shifts suggest that such homogeneity will not last. Populations are shifting throughout the country, and individuals who have historically settled in coastal areas and in the southern most regions of the country are relocating to more northern and interior states in the United States.

One need only look at primary and secondary education to get a glimpse of the types of changes we can see approaching in the next 20 years in terms. The number of non-white, disadvantaged and/or disabled children in public schools in this country is on the rise. The number of individuals primarily speaking a language other than English has increased 1.5% since the 2000 Census and one third of these individuals report "not speaking English very well." Schools are increasingly including bi- and multi-lingual programming in the academic environment to both accommodate non-native English speakers as well as to increase the language proficiency of English speakers in other languages.

These demographics have "tangible financial implications for the operation of a business." The purchasing power of these diverse populations is also on the rise. The amount of disposable income controlled by non-white households continues to grow faster than that of white households. Hispanic buying power alone was expected to reach nearly $800 billion in 2007. Understanding how and where these emerging markets spend their money should be a key component of economic research in the veterinary profession. Unfortunately, concrete data is not available on pet ownership in among non-white populations in this country; however, case studies following national episodes such as Hurricane Katrina, indicate a potentially rich market among these populations to be tapped by veterinarians. A practice's ability to understand communities, changing demographics and how to access emerging and growing markets is critical to seizing the economic benefits of diversity. Customers rely on accessibility, reliability and trustworthiness in patronizing businesses as much as they do when considering price points. A practice's ability to meet these changing needs in a changing demographic will, in short, make a more profitable business.

LONG-TERM STRATEGIES

"A true commitment to diversity requires a long-term, integrated program." Diversity must be ingrained in the organizations structure and culture, which can only happen over an extended period of time. Efforts to recruit and develop a diverse staff and resources take years. In bridging both internal and external practice needs, managers must pursue constant reinforcement of positive diversity outcomes for staff and clients. In setting and implementing strategies for equitable management, team building and positive client interaction, companies establish a demonstrably superior level of service that has financial implications. Moving beyond short term commitments allows business to fully develop an environment that has unquestioned credibility. Diversity efforts should be considered a part of the base business plan and general operating expenses. Like other business components, diversity pursuits require a financial commitment to create sustainable activities. Including them in the bedrock of planning ensures that the diversity efforts become endemic to the organization. These efforts should not be "add-ons." Diversity efforts must be considered potentially high yield investments.

At their core, businesses exist to fulfill the needs of the surrounding community. Assessing and meeting community needs must be inclusive of diversity considerations. These efforts and considerations should not be viewed as a politically correct financial drain, but rather a fundamental good business practice that has a beneficial yield. The research is clear; businesses that embrace diversity efforts—in hiring and management practices as well as in consumer interaction—are more successful. As the country's population continues to evolve, the economic realities of diversity create a compelling argument for embracing diversity initiatives in practice.

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MEETING SOCIETAL OBLIGATIONS AND ENHANCING THE HUMAN–ANIMAL BOND IN PRACTICE

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Alternate Titles: The Veterinarian's Oath in Action or What has Richard done lately to help Society and the Human–Animal Bond?

VETERINARIAN'S OATH

"Being admitted to the profession of veterinary medicine, I solemnly swear to use my scientific knowledge and skills for the benefit of society through the protection of animal health, the relief of animal suffering, the conservation of animal resources, the promotion of public health, and the advancement of medical knowledge. I will practice my profession conscientiously, with dignity, and in keeping with the principles of veterinary medical ethics. I accept as a lifelong obligation the continual improvement of my professional knowledge and competence."

Preventing pain and suffering in companion animals is a legitimate way of using my scientific knowledge and skills for the benefit of society through the protection of animal health. I am attempting to prevent pain and suffering in a few ways, including the HOPE Project, the Pet Safe Project, an organization called PALS (Pets are Loving Support), and educating breeders in the mid-west (the source of many of the puppies purchased in the US). I have also learned I should pay much more attention to the dental needs of my patients and practice preventative medicine and surgery. Along the line of preventing problems in dogs and cats, I have created a handout for owners called True Prevention.

THE HOPE (HELPING OVERPOPULATION THROUGH EDUCATION) PROJECT

The HOPR Project is an extracurricular, voluntary spay/neuter program I created at the University of Missouri. We do this in conjunction with a non-profit organization called Spay Neuter Kansas City. We do low- cost surgeries and address basic preventative needs for dogs and cats belonging to low income people in the Kansas City area as well as doing some feral cat surgeries. The owners get care for their dogs and cats that they couldn't ordinarily afford, we make a dent in the kitten and puppy excess, and our students get valuable experience in the two most common surgeries most veterinarians will perform. This program is a true win/win situation from my perspective. I believe helping to deal with the overpopulation issue in our own little corner of the world is in keeping with the spirit of the Veterinarian's oath.

PET SAFE

Pet Safe is a program the University of Missouri, College of Veterinary Medicine has offered since shortly after I arrived there eight years ago. It is patterned after a program developed at Purdue. We offer boarding, vaccines, and minor health and preventative care for animals of "people in crisis," such as people who have had a house fire, suffered from domestic abuse, etc. Supposedly, we offer free boarding and care for "3 weeks." The 3 weeks often turns in to longer stays than that and unfortunately some owners are not able to take their animals back. We have been highly successful in finding new homes for these animals. We require the pets to be referred to us by some one on the "human side"—eg, a deputy sheriff, directors of women's shelters, a counselor, a pastor—so that hopefully the people's needs are being met by people with expertise in dealing with human matters while we deal with the animal side of the equation. Confidentially is necessary for our safety, the safety of the animals, and the people affected when domestic abuse is the crisis. Domestic abuse is our most common reason to have a dog or cat (or dogs and cats) enter our program.

PALS (PETS ARE LOVING SUPPORT)

PALS is a student-run organization at the University of Missouri College of Veterinary Medicine and I am their faculty advisor. Recently, we have started getting more people from the community involved, including one MD with a visitor dog. This is basically a dog visitation program and we have strict requirements and built-in safe guards to protect the human patients and the dogs. We have far more demand than we can meet and our visits are highly anticipated events particularly by the children and elders we visit. However, we have observed the staff at the facilities we visit are also enthused about the dogs coming to visit. We have had some students start a similar program in their new communities after graduation!

TRUE PREVENTION

One of my missions, as a veterinarian, is to practice preventative medicine and surgery rather than just "Fire Engine" medicine and surgery. Most of us remember the old saying, "an ounce of prevention is worth a pound of cure." I have created an owner handout to try and address prevention called True Prevention. True Prevention Handouts can be obtained electronically by emailing me at: meadowsr@missouri.edu

CONTINUING EDUCATION

"I accept as a lifelong obligation the continual improvement of my professional knowledge and competence". I am obviously "preaching to the choir" here when I say that I think we should all concentrate on education. However, I am talking about education for you, your staff, and your clients. A simple question to ponder: Would you rather it be you or the Internet educating your clients? We are in the "Information Age" and most of us have experienced an owner(s) coming in with their Internet search results in hand, thinking they need us only for our power to script out drugs (to the cheapest source). After a decade in private practice major "CE" (for me) was a solution to professional burn

out. It revived my enthusiasm for our proud profession and I haven't looked back since.

One particular area to strongly consider educating the general public about is the considerable and growing body of evidence showing that humans and companion animals can benefit from each other **physically and emotionally**. The "proof" of this is not anecdotal anymore! We are social animals and we need to be needed. We can benefit from the unconditional love our companion animals give us!

THE ADVANCEMENT OF MEDICAL KNOWLEDGE

As I said, a growing body of evidence is available regarding the benefits of humans and animals interacting. For a start you can go to: http://www.deltasociety.org/AnimalsHealthGeneralReasons.htm We need to contribute information on this important topic as we are able as well as letting the general public (and legislators) know about this. For my part, here is a brief summary of a study I have contributed to.

HUMAN–ANIMAL INTERACTION STUDIES

The Pet a Pet Study, by Richard Meadows, DVM, DABVP, and Rebecca A. Johnson, PhD, RN, was a study of the neurochemical changes that occur in dogs and people when they interact in a quiet, friendly manner. It was an extension of the ground-breaking work done by Johannes Odendaal. Suffice it to say Dr. Odendaal and Dr. Johnson and I both found beneficial chemical changes occurring in both the dog and the people in as little as 15 minutes!

Cost Savings

Companion animals are often viewed as "members of the family" (Cohen, 2002), sometimes too much so for my own personal tastes. However, there have been several studies that have consistently and repeatedly showed lower health care costs for people who own pets than for people that don't own pets. For instance, Bruce Heady found significant healthcare cost savings to the Australian government. He has extended his investigations to Germany and China, where he found similar results not yet published. (His original work was published in Social Indicators Research 47: 233-243, 1999.)

COMMUNICATIONS

A "new" area of CE for me – we all have to do it and our profession is becoming more aware that doing a good job of it is beneficial to our patients, our clients and even US. One good thing to communicate to owners—You value them and their pets. Show owners you value them and their pets

FLIP SIDE: DON'T BE SHY ABOUT POINTING OUT THE VALUE YOU PROVIDE

In my opinion, veterinarians are notorious for not letting people know about financial breaks they gave the owners or efforts "above and beyond" they have gone to for the benefit of the animal and the owner. The flip side of that is what Mary Ann Vande Linde says: "The Number 1 reason clients leave a veterinary hospital or clinic is indifference or poor attitude." Susan Keane Baker says we have two types of value to bring to our clients—emotional value and rational value. She has also brought our attention to some great questions form Andrew Epstein, MD. "Have I addressed your concerns? Do you know what to do next? Do you know what I am going to do next? Do you know what to do if things don't go as planned?"

There many venues and many excellent speakers/resources out there to learn communications from. If you think you can't learn/improve, think again! A few of them include Mary Ann Vande Linde, DVM VMC, Inc. mvandelinde@vmc-inc.com, Susan Keane Baker, www.susanbaker.com, VLE – Veterinary Leadership Experience, IHC – Institute for Healthcare Communication, Effective Communications in Veterinary Practice (see Vet Clin North Am Small Anim Pract, Vol 37, No. 1, January 2007). Three of my long-term favorite articles on client communication are Haas KB, "Clientspeak" vs "Vetspeak" (JAVMA Vol 198, No. 8, April 15, 1991. pp1344-1345); Armistead WW, "Attitude." (JAVMA Vol. 220, No.12, June 15, 2002. p 1817); and Miller LF. "Developing Client Relationships." (Feline Pract. Vol. 27, No.1, Jan/Feb. 1999. pp 5 and 21).

VETERINARY MEDICAL ETHICS

"*I will practice my profession conscientiously, with dignity, and in keeping with the principles of veterinary medical ethics.*" Remember the Golden rule: Treat others (people and animals) as you want to be treated – unless of course you are into pain and abuse – then consider getting professional help. OR as said in the excellent book, *How Full is Your Bucket?*— Treat Others as They Want to Be Treated. I think it is our ethical duty to be the pet's advocate. In the late Dr. Armisted's view you should show you care and avoid the appearance that the owner's animal is just another case to be dispensed with quickly. I believe we need to avoid the appearance of being in a hurry, suggest the best (with conviction) and not worry about the rest!! BUT, we definitely need to remember, No means NO and, at least for now the animals are still the property of the owners. If the owner can't or won't consent to the very best of care (eg, MR scans for a dog that seized) we should offer alternatives when necessary. I believe that veterinarians and their employees (as a general group) are notorious for recommending what they think a client can afford, rather than what they think is best for a pet. Don't judge your client's pocketbook! Is it ETHICAL for a veterinarian not to recommend what is best for a pet? I find a way to suggest the best by worrying about the pet's medical/surgical needs and letting the owner worry about finances is to say "From a medical standpoint, Ms. Jones, Fluffy NEEDS –". If she wants to discuss finances or other less expensive, or less aggressive options I do so in a straightforward, honest, and non-apologetic manner. What I am hoping for is a dialogue in lay English with mutual respect between me and the interested parties. This could also be summed up as: Offer all options, Don't Assume and Show Empathy.

MEDICAL MISTAKES

Medical mistakes are a real challenge to our veterinary medical ethics. My personal approach – tell the truth, tell it the first time, and tell it with empathy, concern and a willingness to do what is right and ethical. If that causes me to get sued, that is why I carry professional liability insurance. You must also be prepared to calmly listen to what the owners say.

WHEN THE BOND FAILS: ABUSE, HOARDING, AND RELINQUISHMENT

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The Association of Human–Animal Bond Veterinarians defines the *human–animal bond* as the relationship between people, animals, and their environment. In most cases, the term is perceived to refer to a situation that is a positive one. Veterinarians focus on providing education, resources, and support to clients, the public and other professionals to create, enhance and sustain an ethical and mutually satisfying relationship between animals and people. When a positive bond has formed, not only do we feel good emotionally, there is scientific evidence that there are physical benefits as well. Much attention has been given to medical research that reveals that pet ownership can lead to a reduction in stress, blood pressure and the number of visits to the doctor's office. There has been widespread publicity about the value of pets for troubled children, the elderly, and people suffering and recovering from major clinical illnesses such as heart disease and depression. We hear that pets are increasingly considered to be members of our families. We give them gifts, celebrate their birthdays, take them with us on vacations and to restaurants, and even share our beds with them. The American Pet Products Manufacturing Association (APPMA) estimates that 63% of US households own a pet, which equates to 69.1 millions homes. They also estimate the amount of money spent on pet food, toys, accessories, and veterinary care in the United States in 2006 was 38.5 billion dollars. This certainly paints an appealing picture of the human–animal bond and the life of pampered dogs and cats in the United States.

But what happens to these family members if the bond never forms or fails? The consequences are usually tragic for the animals, resulting in abandonment, relinquishment or abuse. This is the part of the picture that still goes largely unnoticed by both the veterinary profession and the public, but that needs widespread attention.

ANIMAL ABUSE

Animal abandonment and abuse or cruelty can be the darkest consequences of a failed bond. Animal abandonment is defined as animal cruelty specifically in many states. Pets who are the victims of non-accidental trauma or deliberate abuse and cruelty may be presented to the veterinary practice, but the true cause of the problem may remain hidden if the veterinarian is unwilling to accept that possibility. One of the most common reasons that veterinarians fail to identify animal abuse is that they have not been trained to recognize the warning signs. Furthermore, many do not believe it is a problem that they will ever encounter in their practices so they fail to include it in their list of differentials. But DeViney (1983) found that in pet-owning households (in NJ) with a history of child abuse, utilization of veterinary services was consistent with the norms in the non-abusive population. Landau (1999) found that 87% of veterinarians who responded to a survey had treated abused patients; 50% saw one to three cases per year, 60% suspected they had treated animals that had been abused, and 20% had clients they suspected were being abused. An Ohio State University study (Sharpe, 1999) found the mean number of animal abuse cases seen per year was 5.6 per 1000 patients. So while it may be easy to hide abuse from veterinarians by not bringing the animal in for care, it is a mistake to believe abused animals will not be seen in the average practice.

Definitions

Many veterinarians fail to recognize animal abuse because of the various ways it may be defined. The terms abuse and cruelty are often used interchangeably. Even though cruelty is defined by state laws and not by the veterinarian, it can be useful to have a basic understanding of how the terms abuse, neglect and cruelty are commonly used in these cases. While the 1997 American Humane Association (AHA) publication: *Recognizing and Reporting Animal Abuse: A Veterinarian's Guide* defined abuse in one of the chapters as the "willful knowledge of failing to provide care, or awareness of doing something harmful," Vermeulen and Odendaal (1993) proposed a typology of physical abuse that included passive neglect or ignorance as well as active maltreatment that we so commonly think of such as beating, burning, drowning, and so forth. The typology included the lack of food, water, shelter, sanitation, necessary veterinary care to alleviate suffering, and general neglect, as well as categories for emotional abuse. Although neglect was defined in the AHA publication as "unintentional lack of care that comes from ignorance," some states include it in their legal definition of cruelty, which makes it prosecutable. Finally, cruelty was defined generically in the 2006 forensics text by Sinclair, Merck and Lockwood, *Forensic Investigation of Animal Cruelty* as "any act that, by intention or by neglect, causes unnecessary pain or suffering to an animal." By broadening the generic definition of cruelty, veterinarians will be more likely to at least consider the possibility that an animal has been cruelly treated, and to act upon those suspicions. Cruelty does not have to be egregious, deliberate, or intended for pleasure in most states to be prosecuted at least as a misdemeanor offense. But instead of focusing on one's preconceived ideas of what constitutes abuse, neglect and cruelty or the differences between the terms, the veterinarian should understand that cruelty is defined by statute and that the statutory language may encompass all the terms.

The Role of the Veterinarian in Cruelty Cases

Veterinarians are mandated in at least eight states to report cases of suspected abuse or animal fighting to the appropriate authorities, and may suffer penalties for failure to do so. State laws vary and may require veterinarians to have suspicions, reasonable or direct knowledge, or be a "known case" in order to mandate filing a report. The AVMA position statement on reporting animal abuse is that "*veterinarians may observe cases of animal abuse or neglect as defined by federal or state laws or local ordinances. When these situations cannot be resolved through education, the AVMA considers it the responsibility of the veterinarian to report such cases to the appropriate authorities. Disclosures may be necessary to protect the health and welfare of animals and people. Veterinarians should be aware that accurate record keeping and documentation of these cases are invaluable.*" When deciding whether to file a report or educate, consideration should be given to the number, severity and duration of the problems. Good faith reports of suspicions of animal abuse should be filed on the basis of the physical exam and history. Veterinarians must use good judgment in considering how to handle these cases just as they put in considerable time determining the best treatment course for any client. The report only initiates the legal process that launches an investigation to uncover the facts. Veterinarians serve as the medical expert on a team that includes law enforcement, animal control officers, shelters, and prosecutors. As the medical expert, the veterinarian examines, documents, preserves and interprets the forensic evidence only. The prosecutor presents it to the court and it is important to remember that the final determination of cruelty is made by a judge and jury, not by the veterinarian.

The "Link" Between Animal Abuse and Human Violence

When discussing the failure of the human-animal bond, the link between human violence and animal abuse must be explored. Animal abuse usually does not occur in isolation or a vacuum. It is often violent and deadly, and when animals are at risk, humans are at risk and vice versa. It is often stated that animal abuse serves as a sentinel for the early detection of family violence. The recognition that an animal is being abused may provide the first point of intervention in breaking a continuum of violence that includes domestic, spousal and elder abuse as well as other violent crime. Many households with children also have pets, and aggressive acts against a family member, including the family pet, place all the family members at risk, and can spill over into the community.

The studies that provide evidence that this link exists yield some very startling and sobering statistics. Studies by Kellert (1985), Felthous (1977) and Ressler (1988) have shown that 25% of aggressive male prison inmates, 30% of convicted child molesters, 36% of assaultive women offenders, 48% of convicted rapists, and 46% of incarcerated sexual homicide perpetrators had childhood and adolescent histories of animal cruelty. Ascione found in 1998 that 71% of women seeking shelter from an abusive situation reported that their partner had hurt, threatened or killed their pet; 32% of these women reported that one or more of their children had hurt or killed pets. DeViney found in a 1983 study that animals are abused in 88% of homes where physical child abuse occurred. An MSPCA study of men who were prosecuted for animal cruelty revealed that men who abused animals were five times more likely to have been arrested for crimes of violence against humans, four times more likely to have committed property crimes, and three times more likely to have committed drug and disorderly conduct offenses. Merz-Perez found in a 2001 study that violent offenders in a maximum security prison were significantly more likely to have a prior history of acts of animal cruelty than non-violent offenders.

In the case of several highly publicized school yard shootings, prior to the shootings, Kip Kinkel decapitated cats and blew up cows, Andrew Golden shot dogs, Luke Woodham beat and torched his dog Sparkle, Eric Harris and Dylan Klebold mutilated animals, and Michael Carneal threw a cat into a bonfire. Serial killers Jeffrey Dahmer, Albert DeSalvo, David Berkowitz, and Ted Bundy all committed earlier acts of animal cruelty. Kellert and Felthous conducted studies of the childhoods of men in prisons and psychiatric hospitals for criminal behavior and found that there was a significant association between acts of cruelty against animals in childhood and later serious, recurrent aggression against humans. In another study, HSUS estimated that approximately 12% of the reported acts of intentional animal cruelty involved some form of family violence.

There is a strong association between early childhood animal cruelty and later juvenile delinquency, violent adult criminal behavior and conduct disorders. While not all children who commit acts of animal cruelty become criminals or become involved in illegal or violent activities in adulthood, they are more likely to do so than children who do not. In 1966, Hellman and Blackman determined there was a positive and predictive association between a triad of behaviors including bed-wetting, arson, and animal cruelty, and future criminal activity. The FBI has been known to refer to this as the "homicidal triad." Children exhibiting these three behaviors should receive serious counseling and intervention to prevent future acts of violence. A study by Tapia in 1971 also revealed that not all children "outgrow" performing acts of animal cruelty. That study indicated that 62% of the children who entered clinics for treatment for animal abuse and other disorders were still abusing animals 2 to 9 years later. Animal cruelty should not be viewed as just "boys will be boys." In 1964, anthropologist Margaret Mead warned that "the most dangerous thing that can happen to a child is to kill or torture an animal and get away with it." Veterinarians who encounter deliberate animal abuse by children should evaluate it very seriously and discuss it with their parents and encourage them to seek professional counseling. Many experts believe that early interventions can prevent future violence against both humans and animals

Reasons for Animal Abuse

The bond may be broken or never have been formed in cases of animal abuse. There is no single profile that describes the animal abuser. Just as with family violence, animal abuse crosses all socioeconomic lines. Animals may be abused by people for a variety of reasons. Kellert and Felthous provided some of the following reasons: "1) to control the animal, possibly to eliminate undesirable characteristics; 2) to retaliate against the animal for a presumed wrong; 3) to satisfy a prejudice against a breed or species; 4) to instill aggressive tendencies in the animal; 5) to enhance one's own aggression; 6) to shock people and gain attention; 7) to retaliate or get revenge against another person; 8) displaced hostility, 9) nonspecific sadism, including sexual assault." Animal abuse may be used to hurt or control family members. Abused children may perform acts of animal cruelty or even kill their pets to protect them from even worse abuse, to act out aggression against a more vulnerable household member, to act on aggressive feelings toward abusive adults, or because they are imitating the behavior they have observed.

Warning Signs of Animal Abuse

Veterinarians should be aware of the following warning signs that animals may be abused: 1) injuries that could not logically have occurred in the manner that the owner has described; 2) discrepancies or changes in the history; 3) lack of concern about the disposition of previous pets or their (in)ability to care for animals; 4) refusal to acknowledge the seriousness of a condition, provide treatment for or follow-up on treatment of painful conditions that cause suffering; 5) indifference about the cause of an injury; 6) constant parade of new animals; or 7) use of several veterinarians.

A combination of the following physical signs of neglect in one animal or the presence of these signs in several animals may present cause for concern: 1) emaciation; 2) severely matted hair; 3) avulsed and ingrown nails; 4) multiple fractures or wounds in various stages of healing (characteristic of the "Battered Pet Syndrome"); 5) heavy parasite infestations with resultant anemia and skin lesions; 6) collars that are embedded in the neck; 7) overall filth; or 8) bite wounds that are characteristic of dog fighting. Animals who present with problem behaviors such as inappropriate elimination, aggression, noisiness, disobedience, or destructiveness or who are in need of constant supervision are also at greater risk of being abused.

Bestiality/Zoophilia

Bestiality is one of the oldest and rarest forms of animal abuse, yet Kinsey found as far back as 1953 that overall, 8% of the US male population surveyed admitted to having had sexual contact with animals. No one likes to talk about it, but bestiality is currently not illegal in all states. Historically, sexual contact with animals has been punished by society in a wide variety of ways, ranging from death to no punishment at all. In many cases, the animal is injured or dies as a result of the sexual encounter. Sexual assault of animals may occur in a variety of settings. It may be used to satisfy adolescent curiosity about sex, as a substitute for a human sexual partner, or to control more vulnerable family members or children.

Zoophilia is a term that is used for situations in which the person claims to be in a loving sexual relationship with the animal. According to the American Psychiatric Association, zoophilia is defined as a disorder of sexual preference. There are many Internet sites devoted to zoophilia and reason to be believed it may be more widespread than reported. Veterinarians should be aware of this activity because they will be responsible for analyzing the forensic evidence for confirmation of actual sexual contact with and/or cruelty to the animal.

(For more information the reader is referred to Helen Munro's article on sexual abuse of animals as part of the Battered Pet Syndrome [Munro, 2001] or the textbooks, *Veterinary Forensics* by Melinda Merck or *Forensic Investigation of Animal Cruelty* by Sinclair, Merck and Lockwood, 2006.)

ANIMAL HOARDING

Most veterinarians will eventually encounter an animal hoarder. On the surface, people who take in multiple animals may seem to epitomize the human–animal bond at its best, but animal hoarding is a multifaceted problem that often causes true and intense animal suffering. A case definition (taken from Illinois state law) of an animal hoarder is someone who 1) accumulated a large number of animals that overwhelmed their ability to provide minimal standards of nutrition, shelter, sanitation, and veterinary care; 2) denied the deteriorating conditions of the animals and environment; and 3) denied the negative impact of the collection on health and well-being of themselves or other household members. Some experts believe that many hoarders suffer from an obsessive-compulsive or other psychological disorder. Hoarding is not about good intentions gone awry; dead and severely ill animals were found in 80% of cases.

Hoarders are not just the stereotypical well meaning "cat lady." It is true that nearly three quarters of them are women and live alone, but they are represented in every socioeconomic level and many professions, including shelter rescue and foster care groups. Some do have minors living with them. Almost half are over 60 years of age and cats are slightly more hoarded than dogs, although it can be other species as well. They can be very clever and use several veterinarians to escape detection. The Hoarding of Animals Research Consortium (http://www.tufts.edu/vet/cfa/hoarding/) that is studying this problem has provided some warning signs that a client may be a hoarder: 1) perfuming or bathing the pet to conceal odors; 2) using a surrogate pet to get medications for other unseen animals; 3) showing an unwillingness to say how many pets are owned; 4) claiming to have just found an animal in deplorable condition; 5) having a constantly changing parade of pets; 6) office visits for problems related to poor preventive health, filth, overcrowding and stress (fleas, ear mites, intestinal parasites, upper respiratory infections, urine scald); or 7) demonstrating an interest in acquiring more animals.

Veterinarians who suspect their clients may be hoarders should resist the temptation to simply offer discounted and pro bono services because that only serves to enable their behavior and prolong animal suffering; instead they should file a report to get assistance for both the human and animal victims of this problem. Veterinarians cannot handle these cases alone, as treatment or simple removal of the animals from true hoarders never solves the problem. The recidivism rate is 100%. They will always obtain more animals unless there is constant follow up monitoring and counseling. A community inter-agency approach involving the department of health, social services, psychiatrists, law enforcement, animal shelters and veterinarians is necessary to find a resolution to the problem of animal hoarding. For more information go to http://www.tufts.edu/vet/cfa/hoarding/

RELINQUISHMENT

Finally, animals who are victims of an unformed or broken bond often wind up as a "problem" for local humane societies and animal control shelters. The American Society for the Prevention of Cruelty to Animals (ASPCA) National Outreach Department estimates there are between four and six thousand animal shelters in the US. Because there are no federal regulations and few state guidelines governing the operation, definition of or record keeping in shelters, no one knows the exact number. It is known that millions of animals enter shelters and are euthanized every year. While some of these animals are surrendered by their owners for euthanasia (rather than going to their private practice) due to sickness and old age (Kass et al, 2001) shelter euthanasia numbers are still used to measure the magnitude of the pet population problem. While many communities are struggling to reduce the euthanasia of healthy, adoptable animals through the use of aggressive adoption, behavior counseling and spay-neuter programs, one of the highest risk factors for death for dogs and cats in this country remains ending up in an animal control shelter.

The National Council on Pet Population and Study (NCPPS) is a coalition of animal welfare and animal control organizations, breed groups, industry and veterinary professionals, that was formed to conduct studies to determine the "number, origin and disposition of pets (dogs and cats) in the US, and to recommend programs to reduce the number of homeless pets in the US." The Council reached the conclusion that "many human companion animal relationships fail because people have inaccurate and inappropriate expectations of their pet's medical and behavioral needs, and their role and responsibility in providing for these needs." In addition, they determined the top ten reasons for dogs and cats being relinquished to shelters. The list for dogs included: 1) moving; 2) landlord issues; 3) cost of pet maintenance;, 4) no time for pet; 5) inadequate facilities; 6) too many pets in the home; 7) pet illness; 8) personal problems; 9) biting and 10) no homes for littermates. The top ten reasons for cats being relinquished to a shelter included: 1) too many in the house; 2) allergies; 3) moving; 4) cost of pet maintenance; 5) landlord issues; 6) no homes for littermates: 7) house soiling; 8) personal problems; 9) inadequate facilities, and 10) doesn't get along with other pets.

Veterinarians should be familiar with the issues that increase the risk of relinquishment due to a broken bond and be prepared to intervene to keep animals in their homes. They can offer affordable behavior counseling and neutering services, work with the local shelter, encourage adoption of shelter animals and support pet friendly legislation that allows pets in housing, and opposes breed and insurance bans, etc. If all else fails, families that relinquish their pets to shelters should be encouraged to provide the shelter with honest information in order to successfully rehome the animal. Conversely, in shelters with high euthanasia rates where rehoming opportunities are scarce, relinquishers should be provided with a realistic assessment of the chance of their pet finding a new home so the shelter will not be blamed if the animal is ultimately euthanized. The reader is directed to the NCPPSP website at www.petpopulation.org and www.aspca.org for more information on these topics.

CONCLUSION

When the human–animal bond fails or is negative, the consequences for animals can be devastating, often resulting in relinquishment, hoarding or abuse. Whatever fate befalls the animals, the ultimate costs are too high for the profession to ignore. The veterinarian's oath calls for veterinarians to use their skills for the benefit of society through the relief of animal suffering and the promotion of public health; and to practice conscientiously and in keeping with the principles of veterinary medical ethics. Educating clients and the public about responsible pet ownership and care, providing affordable spay neuter, veterinary care and behavior counseling, and taking a leadership role protecting animals is surely as much a part of the professional's duties as practicing quality medicine. When deciding how to manage cruelty cases, veterinarians should always bear in mind that cruelty is defined by statute and the court, not by the veterinarian. In addition to promoting and preserving a positive human–animal bond, by investigating and reporting suspected animal cruelty, veterinarians can also enrich and save the lives of both humans and animals.

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6. For more information on animal hoarding go to http://www.tufts.edu/vet/cfa/hoarding/
7. For more information about forensics, go to www.veterinaryforensics.com

Other references are available from the author upon request.

THE HUMAN–ANIMAL BOND: SOCIETAL OBLIGATIONS IN PRACTICE—PAST, PRESENT, AND FUTURE

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"Being admitted to the profession of veterinary medicine, I solemnly swear to use my scientific knowledge and skills for the benefit of society through the protection of animal health, the relief of animal suffering, the conservation of animal resources, the promotion of public health, and the advancement of medical knowledge..."

The oath taken upon entry into the profession of veterinary medicine suggests that the objectives of the profession have not changed much since the first veterinary school in Europe was founded in 1762 in Lyon, France, but societal changes have induced a transformation in how we achieve those objectives. The purpose of the first veterinary school was to study the anatomy and diseases of horses, cattle and sheep, and its establishment was due in part to efforts to control or cure Rinderpest, a significant threat to livestock in Europe at that time. In that era, the value assigned to domestic animals was primarily utilitarian, and the job of the newly trained veterinarians was to keep the animals healthy so they could fulfill their function in society. Although they may not have been consciously concerned about the suffering of their patients, the discovery of new ways to treat or prevent disease certainly contributed to the relief of suffering.

A UTILITARIAN VIEW OF ANIMALS IN SOCIETY

Although society's Cartesian view denied any intrinsic value to an animal's life other than strict utility, undoubtedly there have always been instances in which humans developed emotional relationships with individual animals. By the late 19th century, a growing animal welfare movement asserted that animals did have feelings and deserved a life as free as possible from pain and suffering. Scientists such as Darwin proposed that animals experienced the same emotions and had the same cognitive ability as that of humans, differing only in degree. Antivivisectionists in the late 19th century and early 20th century challenged the use of animals in research and education. Humane organizations in Europe and America, such as the SPCA (UK, 1824) and the ASPCA (United States, 1866) sought to put an end to the abuse of animals, initially focusing on working horses. These and other groups succeeded in establishing welfare guidelines for the management of domestic animals that continue to evolve. In the late 20th century, the animal rights movement differentiated itself from the animal welfare movement by opposing any use of animals. The term "speciesism" was introduced as "...a prejudice or attitude of bias toward the interests of members of one's own species and against those members of other species."

This is a cursory review of the changing relationship between humans and non-human animals, and it serves as background to the discussion of how these changes affect the obligations of veterinarians to society.

THE EMERGENCE OF THE HUMAN–ANIMAL BOND

British author Alfred Wight (under the pseudonym of James Herriot) published a number of books about the life of a veterinarian in a small village in Yorkshire in the middle of the 20th century. The immense popularity of these books, and the accompanying television series, confirmed that, by the second half of the 20th century, the emotional ties between humans and animals were not only growing in strength, but that these relationships encompassed the veterinarian.

In the late 1970s a name was applied to the emotional connection between humans and companion animals: the human–animal bond. Efforts were expanded in an attempt to further define the affinity humans had for their pets. (See, for example, studies by Stallones, Johnson, and Staats.) Researchers began to confirm the positive effects companion animals could have on human health (see overviews by Wilson, Wilks, and Becker), the beneficial effects of pets on the development of children, on people with disabilities, and on older pet owners. Companion animals are increasingly called upon to work as service animals, providing eyes, ears and mobility to those with visual, hearing or other physical disabilities, and to work as therapists for the infirm, the elderly and in psychosocial interventions. Work by Odendaal suggests a reason for the benefits of the interactions between humans and companion animals. He demonstrated that brief, positive interactions between dogs and their owners result in increased β-endorphins, oxytocin, prolactin and other neurochemicals that are associated with affiliation or bonding *in both species*. In humans, cortisol decreases, indicating the stress-reducing potential of the human-animal bond.

Surveys have been conducted to elucidate the impact of the human–animal bond on veterinary practice. Catanzaro investigated the level of awareness veterinarians' had of the social interdependence between clients and their pets and found that veterinarians routinely underestimated that bond. Twenty years later, a small study was conducted in Sacramento, California, to see if there had been any change, only to find that veterinarians continue to underestimate the relationship between client and pet. (R. Timmins, 2006, unpublished data) Studies sponsored by the AVMA have shown that not only does the vast majority of pet owners consider their pets members of their families, but a significant portion think of them as children. This is the basis for applying the term *Veterinary Family Practice* to primary care veterinary medicine. The nature of the bond affects how frequently the client brings the pet to the veterinarian and how faithfully the client complies with the veterinarian's recommendation. Other work emphasizes the unfortunate results of a suboptimal bond: relinquishment, convenience euthanasia, animal abuse, and animal hoarding.

CHANGES IN SOCIETY INDUCE CHANGES IN THE VETERINARY PROFESSION

How has the veterinary profession responded to the dramatic changes in human–animal interactions? Of course, the mandate to protect the food supply remains critical to the well-being of society, but the number of food animal practitioners continues to decline (although it is thought that the decline in supply is greater than the decline in demand). A large majority of veterinarians are now in companion animal practice, whereas just 50 years ago, the small animal practitioner was a rarity. Clients are offered advanced technologies and specialized medicine and surgery for the pet members of their families. It is predicted that the demand for companion animal practitioners will rise significantly over the next decade.

Recognizing that globalization presents challenges to the availability and safety of our food supply and that bioterrorism is an emergent threat, the profession acknowledges the need for an increased focus on public health and greater preparation for the invasion of foreign animal diseases and zoonoses. Approximately 75% of newly emerging human diseases have an animal origin, giving rise to the concept of One Medicine/One Health, which refers to the overlap between human and veterinary medicine. These issues are relevant to the veterinary family practitioner who has frequent and direct involvement with the interaction of humans and animals.

CURRENT CHALLENGES TO MEETING SOCIAL OBLIGATIONS

How can veterinary family practitioners today meet the obligations to society imposed by the veterinary oath?

"...through the protection of animal health..." It is incumbent on the veterinarian to offer services based on wellness surveillance and prevention instead of repair shop services. This involves developing individualized, life-long health plans based on risk assessments that take into consideration genetics, behavior, nutrition, environmental exposures and the pet's role in family. Veterinarians must work to understand the nature of the attachment between clients and their pets and develop strategies that encourage optimal bonding. Finally, protecting animal health demands offering the best available care, and advocating for the client and pet during the referral process.

"...the relief of animal suffering..." Educating clients about the needs of pets requires application of the principles of adult education, understanding learning preferences, and using skillful clinical communication. Clients must be taught how to avoid harmful anthropomorphism by focusing on the true needs of the other species that share their home. In the community, the veterinary family practitioner must be a leader in animal-related issues.

"...the conservation of animal resources..." As animals play a more significant role in promoting human health and well-being, "animal resources" take on a new meaning. Animals serve as assistants to people with a variety of disabilities, are involved in therapy programs, and promote health and longevity in the people they live with. Dogs especially, take on new burdens in Search & Rescue, police work, border patrol and other scent detection work. Protection of these resources requires a greater understanding of the job demands placed on these animals in their new roles. It also requires an understanding of the special needs of the pets' owners and an ability to meet them. The veterinary family practitioner must raise the community's awareness of and appreciation for the true value of these companions.

"...promotion of public health..." The intimate relationships between pets and their human family members increase the risk of zoonotic disease. Risk communication goes beyond rabies, intestinal parasites, ringworm, toxoplasmosis and other zoonoses spread by companion animals. The publicity afforded avian influenza and West Nile virus has made society more acutely aware of the overlap of human and animal diseases. It has been suggested that pets may serve as sentinels for some emerging diseases, such as avian influenza. (Cats have acquired this disease in Germany and in Malaysia.) The veterinarian must help communities and their clients understand these risks and how to manage them.

"...the advancement of medical knowledge..." There have been tremendous advances in knowledge and technology. Pet owners are in dire need of trusted advocates, who can serve as interpreters and guides when healthcare requires complex diagnostic or therapeutic interventions.

FUTURE CHALLENGES TO MEETING SOCIAL OBLIGATIONS

Clients with Special Needs

As pet-loving baby boomers age, an increasing percentage of clients will be geriatric. Increasing age is associated with increased disease incidence and attendant medications, visual and hearing deficits, varying degrees of cognitive impairment, mobility restrictions. Veterinary family practitioners must address these factors when considering diagnostic and therapeutic options.

As companion animals (especially dogs) are tapped for a greater variety of service and therapeutic roles, both the animals and the owners will have particular needs that will affect the health care of the pet. Veterinary services must be expanded to accommodate these needs.

A Changing Legal Atmosphere

Emotional attachments are increasingly recognized as a value to the pet owner. It is highly likely that courts will allow financial awards in cases of malpractice or neglect. Veterinarians must be actively involved in promoting policies that manage these types of awards. They must also focus on developing expert clinical communication skills in order to avoid or minimize the emotional and financial impact.

Animal Rights

Veterinary family practitioners must be proactive about reclaiming leadership in the area of animal well-being. As the emotional connection between humans and animals continues to deepen, humans will become more susceptible to the well-intentioned but uninformed promotion of policies and laws that may actually be harmful to the animals.

Increasing Emotional Attachments

Psychologist Boris Levinson noted in 1965 that "…it would be helpful for everyone concerned if the veterinarian were sufficiently trained in the behavioral sciences to recognize the complex factors operating in these [human–animal interactions]…the veterinarian needs special training to provide the most skilled help to such situations." Clients will have greater need of emotional and sometimes psychological support that will become apparent during interactions with their veterinarians. There must be an increasing collaboration between veterinary medicine and human mental health and social services professionals.

Rising Cost of Care

As the technology of veterinary medicine becomes more complex and more expensive, veterinarians will have to address the issue of helping clients pay for veterinary services.

One Medicine

Veterinarians must work closely with medical professionals in the human field in order to increase understanding of the interrelationship between human and animal health. This includes zoonotic disease, but also refers to the other health-promoting aspects of companion animal ownership.

Community Leadership

Meeting all of the challenges listed above requires a greater emphasis on training in the areas of leadership, conflict management, media communications, and clinical communication. Community service should be an important part of veterinary family practice.

Undoubtedly, there will be other unanticipated challenges facing the profession. To rise above them and to meet the profession's social obligations, veterinarians will need more than superb technical diagnostic and therapeutic skills. There must be a greater emphasis placed on skills necessary to understand and support the roles animals play in society and in families.

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THE ADVANTAGES OF THE CT SCAN OVER MYELOGRAPHY FOR THE HERNIATED DISK: A REVOLUTION

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Disk herniation is one of the most common cause of neurologic dysfunction in dogs. When moderate to severe neurologic signs are obvious, an early surgical treatment is required. Historically, myelography has been used as a diagnosis tool for the proper localization of herniated disks but many complications are described. Our goal is to discuss the advantages of the CT scan over myelography for the diagnosis of herniated disks.

COMPLICATIONS ASSOCIETED WITH MYELOGRAPHY

Adverse effects associated with intrathecal injection of contrast media have been widely reported and included seizure, apnea, worsening of neurologic status, cardiac arrhythmias, meningitis, subdural injection, hyperesthesia, hyperthermia, vomiting, asystole, and death.

Metrizamide was the first water-soluble, nonionic contrast medium used for veterinary myelography. Frequency of seizure after myelography with metrizamide has been reported to be between 15% and 51%. Iohexol is a second-generation, nonionic contrast medium that is less epileptogenic but seizures are reported in 2% to 21% of patients. Deterioration of neurologic status the day after myelography is the most common complication. Although the reason for this deterioration is not exactly known, it has been attributed to the contrast medium toxicity. Dogs with caudal cervical myelopathy, extradural tumors, and meningitis have a greater likelihood that their neurologic status will worsen the day after surgery. The second most common complication is seizure. Several factors are reported to influence the development of seizures including the site of injection, with the lumbar site having a decrease incidence, number of intrathecal punctures, and breed. The worst complication is an asystole during the myelographic procedure; in our experience, this complication has occurred most commonly in patients with myelomalacia.

Spinal fluid puncture is not an innocuous procedure. Adverse effects of myelography are related to the technique, constitution of the patient, and pharmacologic factors of the contrast medium. Complications may be associated with mechanical effects of routine lumbar subarachnoid puncture. Spinal cord compression occurs because of marked indentation of dura as the needle is advanced through the dural membrane. A tenting of the dura is reported during subarachnoid puncture. Misplacement of the spinal needle and subsequent intramedullary injection of contrast medium is a serious complication. Transmedullary lumbar spinal puncture has been associated with transmedullary injection at L4-L5 or L5-L6. Neurologic deficits are observed infrequently unless intramedullary injections occur. Fluoroscopic guidance is then recommended to ensure needle placement within the subarachnoïd space.

Despite of the steps taken to prevent complications, myelography remains a potentially dangerous, even lethal technique. A safer, less invasive technique would be greatly beneficial to our patients.

ADVANTAGES OF THE CT SCAN

Access to computed tomoraphy (CT) is now standard in academic institutions and specialty practices. Using up to date equipment (third- and fourth-generation scanners), imaging of the vertebral column using CT is quick and produces transverse images of the vertebral canal that can be reconstructed in other planes. Computed tomography has been used successfully to image the brain, the lumbosacral junction, neoplasia, and the cervical spine of caudal cervical spondylomyelopathy. The presence of herniated disk material in the vertebral canal is apparent on CT scan, without the injection of the subarachnoid space, even in animals where little disk material is herniated. There are several advantages to using non-contrast CT images to identify disk herniations. It is a noninvasive diagnostic technique that is not associated with side effects seen following myelography. The speed with which a diagnostic CT scan can be done, approximately 10 minutes, is also beneficial to the animal under general anesthesia for diagnosis and surgery. The risk of systemic hypotension is higher under general anesthesia and hypotension can reduce blood flow to the injured spinal cord, thus minimizing the time under anesthesia is important.

Images should be viewed initially using soft-tissue parameters and then subsequently using bone parameters. The normal spinal cord has intermediate attenuation on transverse images equivalent to that of soft tissue such as adjacent kidney. Spinal cord causes more attenuation than epidural fat, which is usually most evident at the level of the disk space, especially adjacent to the intervertebral foramen. Displacement of epidural fat at this level, or an increase in the attenuation characteristics of the epidural fat, is a useful indicator of a disk extrusion. Another very common feature is the presence of a focal, heterogeneous, hyperattenuating mass of mineralized disk material in an epidural location. A less common presentation occurs when disc material and blood are spread more diffusely along and around the spinal cord. In such cases the epidural mass is relatively small in individual transverse images and is only slightly more attenuating than the spinal cord. It does, however, still cause more attenuation than epidural fat, which is either displaced or infiltrated with blood and nuclear material. In some animals a rim of increased attenuation is visible around the spinal cord, which almost certainly represents epidural or subdural hemorrhage.

The exact appearance of hemorrhage may depend on how recent it is and if the hemoglobin has degraded. Adjacent chronic disk lesions, which are frequent and often incidental findings in dogs with acute extrusions, are recognized by their extreme hyperattenuation, which may approach that of cortical bone. The degree of attenuation can be quantified by measuring the Hounsfield units (CT numbers) within a defined region of interest.

For dogs with suspected cervical disk extrusions, the scan extends from the mid-atlas (useful to help rule out atlantoaxial instability by demonstrating a normal dens) to cranial T1 vertebra. Attenuation characteristics of cervical disk extrusions in chondrodystrophoid breeds are similar to those seen in the thoracolumbar area except that extruded disc material rarely extends over more than one vertebra and diffuse, subdural hemorrhage is unusual. Reconstruction techniques can be used to enhance further the diagnostic value of CT in disc disease as well as for other conditions.

Comparisons between CT and magnetic resonance imaging (MRI) in humans show that each has its own strengths and weaknesses. CT is superior for identifying (cervical) fractures, whereas MRI is better for soft tissue lesions.

The duration of the herniation may also be appreciated on CT images in dogs with long-standing history of disk herniations; disk material identified in the vertebral canal has a more hyperattenuating appearance than recently herniated disk material.

In the absence of disk herniation following a CT examination, it is, however, recommended to perform myelography to completely expose the spine. Myelography allows the identification of a few abnormalities not seen on CT images, such as myelomalacia, hematomyelia, and myelodysplasia.

In conclusion, herniated disk and hemorrhage can be identified quickly and very safely in dogs using CT without the numerous adverse effects of myelography (Figures 1–6).

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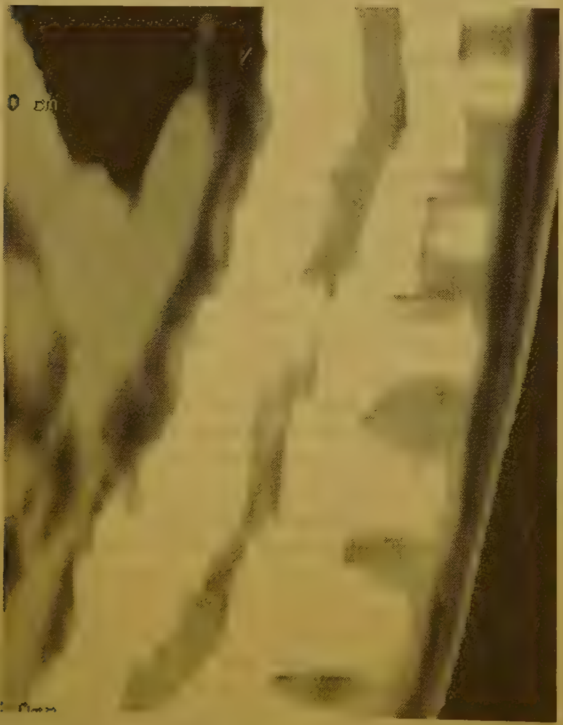


Figure 1. Reformatted sagittal view of a French bulldog with a L2-L3 herniated disk.

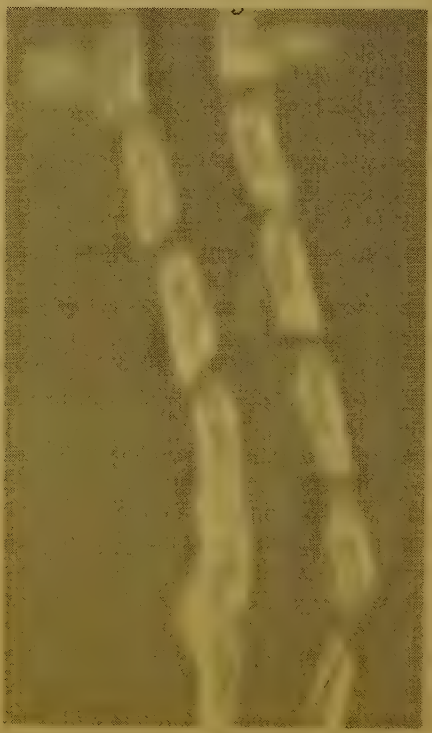
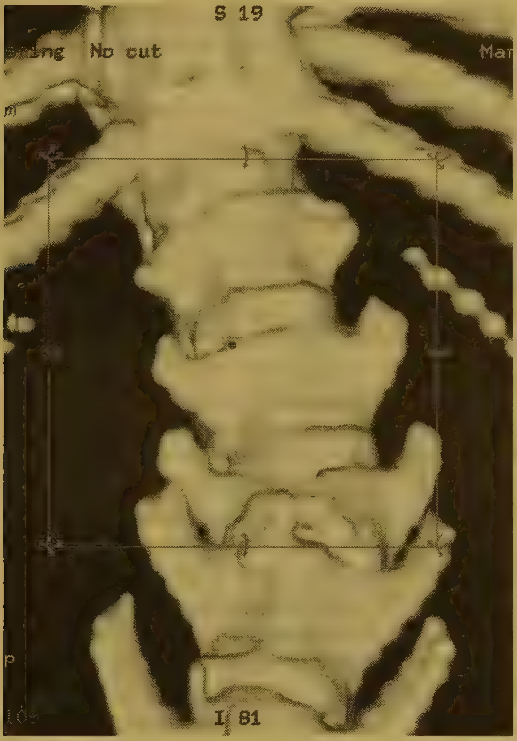


Figure 2. Same dog as in Figure 1 with a bone filter. Note the right L2-L3 herniated disk with an associated caudal hematoma.



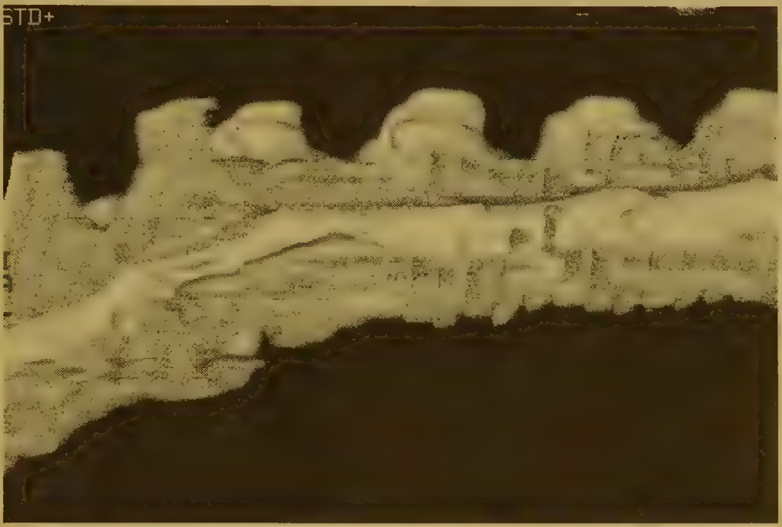
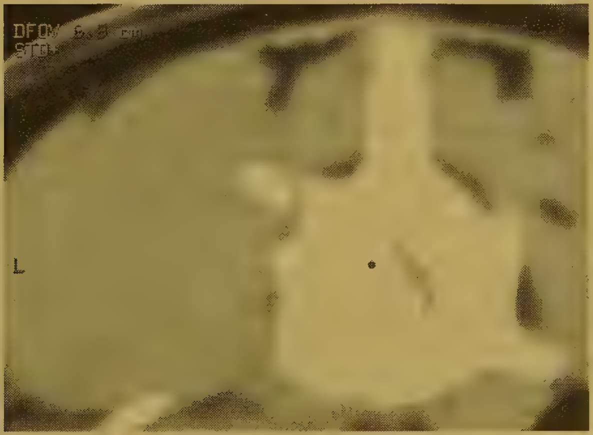


Figure 4. Right half 3D view of the same dog as in Figure 1. Note the herniated disk in the vertebral canal.

Figure 3. Ventral 3D view of the spine of the same dog as in Figure 1.



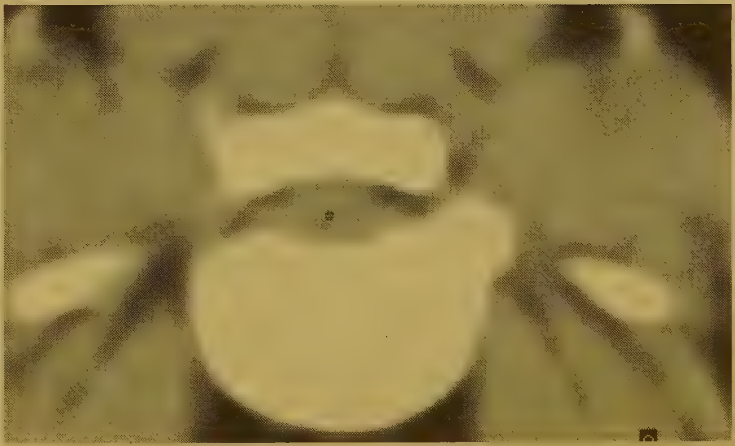


Figure 5. Axial CT showing a voluminous herniated disk.
Figure 6. Foraminal herniated disk.

IMAGING JOINTS – A SURGEON'S PERSPECTIVE

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Reaching a diagnosis for lameness in the dog is frequently more problematic in the forelimb than the hindlimb. As a result, our reliance on imaging for helping to reach a definitive diagnosis is encountered more often in forelimb lameness. For that reason we will focus on the forelimb during this discussion.

Methods of imaging the forelimb include:

- Radiology
- Ultrasonography
- Magnetic resonance imaging
- Arthroscopy

In these general comments, only radiology will be considered as it is often all that is required or available in general practice.

Having decided where the clinical suspicions of lameness rest it is important that the clinician either takes the radiographs or is an attendance at the time of the study. All too often a request is made for, say, elbow radiographs of a dog's left limb carried out by a second ("uninformed") clinician. When these are normal, the second clinician might think to radiograph the shoulder but after that the investigation will probably be halted. To get the most out of such an investigation it is important that the clinician in charge of the case is present.

If a particular joint is suspected then the investigation should obviously focus on that joint, but in the case of the shoulder or elbow a view of the other joint might be worthwhile "just to be sure." If the suspected joint appears normal, then take survey radiographs of the rest of the limb: mediolateral shoulder; mediolateral elbow; dorsopalmar carpus/manus ("landscape views" to include the bones) +/- the cervical/cervicothoracic vertebral column. If anything potentially significant is found then the clinical signs may need to be reviewed before over-interpreting the radiographic changes. In addition, if the suspected joint is normal then it may be worth radiographing the contralateral joint since any pathology found might be bilateral but the changes might have yet to develop in the lame leg.

SHOULDER

Radiology

A **mediolateral** view is the easiest to take and provides an enormous amount of information, being all that is required in many disease processes (eg, osteochondritis dissecans [OCD], neoplasia). However, in adult dogs with nontraumatic and non-neoplastic causes of shoulder lameness, the results of plain radiographs can be disappointing and should not be over-interpreted. Often there will be evidence of degenerative pathology with osteophytes present on the margins of the humeral head and superimposed on the greater tubercle, but these changes are seen in many radiographs of shoulders belonging to middle-aged dogs.

A **caudocranial** view can add to the information gained from the mediolateral film and is particularly useful in conditions such as infraspinatus contracture (or luxation) but the same view of the contralateral limb should be made for comparison.

Special views would include stressed, rotated and tangential radiographs. **Stressed** radiographs are predominantly to establish the direction of a luxation. **Rotated** views may detect such lesions as OCD not seen in a standard mediolateral view. **Tangential** views are generally to skyline the intertubercular groove (in which sits the biceps tendon) and this may help to show that osteophytes seen superimposed on the greater tubercle in a mediolateral view are actually medial to the greater tubercle and, therefore, could be interfering with the biceps tendon.

Arthrography involves the introduction of a contrast agent into the shoulder to delineate the articular margins. Any sterile contrast agent can be used but the author uses Omnipaque 300 (diluted 50:50 with sterile water for injection). If exploring the articular cartilage (eg, suspect OCD) then about 2 mL of agent should suffice. In adult dogs when looking for problems such as bicipital tenosynovitis, a dose of about 5 to 6 mL in a 30- to 35-kg dog would be more appropriate.

How reliable is radiography in making a diagnosis in common/well described causes of nontraumatic shoulder lameness?

Very Reliable

- Osteochondrosis
- Osteochondritis dissecans if including arthrography or flap is mineralized
- Developmental luxation
- Neoplasia
- Osteoarthritis (?)

Intermediate/Helpful

- Infraspinatus contracture
- Specific sites of mineralization to explain point pain, eg, supraspinatus insertion, infraspinatus bursal ossification

Unreliable

- Bicipital tenosynovitis (some cases will show definitive changes with arthrography and osteophytes medial to the tubercle on tangential view increases level of suspicion)
- Glenohumeral ligament pathology

Ultrasonography

Ultrasonography has been used to look particularly at the biceps tendon but is of limited practical value from a diagnostic point of view.

Magnetic Resonance Imaging

Studies are currently underway to try to establish the "normal" MRI appearance of the shoulder, but this modality is not currently used as a diagnostic aid. The exception may be in cases suspected of having brachial plexus tumor where MRI may demonstrate enlargement of a nerve root that is too peripheral to be seen myelographically; however, there are certainly false negatives from such a study.

Arthroscopy

In recent years this modality has been used increasingly to investigate shoulder joint lameness, particularly in the adult dog. From this a number of conditions are now recognized (eg, glenohumeral ligament tears) that would formerly have been grouped, along with bicipital tenosynovitis, as "rotator" or "cuff" tendon and ligament problems. Although this has not yet led to established techniques for treatment, it has to be hoped that being able to make a more accurate diagnosis is the first step in developing a rational treatment.

ELBOW

Radiology

Although a **mediolateral** view will serve as a screen for periarticular osteophyte formation, a **craniocaudal** view is often invaluable in detecting either changes at an earlier stage or abnormalities that are not seen in the first view. The mediolateral view is generally taken with the joint in a "neutral" position but flexed views can be useful for looking at the borders of the anconeal process or assessing changes in lesions of the medial epicondyle. In most practices a craniocaudal view of the elbow is usually taken with a vertical beam x-ray. This usually creates a slight obliquity in the view (craniomedial-caudolateral). Although such a view can be more useful than a true craniocaudal (eg, for viewing the medial coronoid process) the converse can also be seen. Therefore, survey radiographs of an elbow suspected of being the source of lameness might include mediolateral and craniocaudal views (the latter including views taken with both a vertical x-ray beam and a horizontal x-ray beam). Additional information may then be gained from taking **flexed** (eg, anconeal process, epicondylar lesions) or **oblique** views (eg, condylar fissure).

Arthrography

Arthrography is rarely indicated.

How reliable is radiography in making a diagnosis in common/well-described causes of nontraumatic elbow lameness?

Very Reliable

- Developmental luxation
- Ununited anconeal process
- Osteochondritis dissecans – but only if mineralized flap seen
- Medial epicondylar lesions
- Osteoarthritis

Intermediate/Helpful

- Coronoid disease
- Incomplete fracture / ossification of the humeral condyle

Unreliable

- Fragmentation of the coronoid process

Ultrasonography

Not utilized.

Magnetic Resonance Imaging

MRI is currently used infrequently to investigate elbow lameness. Possibly the most "common" reason is when incomplete fracture/ossification of the humeral condyle is suspected but cannot be demonstrated radiographically. Computerized tomography is also able to help make such a diagnosis.

Arthroscopy

Common diagnoses such as elbow dysplasia can usually be made from plain radiographs but definitively establishing the presence of OCD or fragmented coronoid process often requires either arthrotomy or arthroscopy. Furthermore, not all dogs with dysplasia produce the secondary changes that serve as markers of articular pathology. The advantage of arthroscopy relates to being able to look at more of the articular surface, and a lower morbidity, particularly if no abnormalities are found. As a result it may allow earlier diagnosis and treatment of such conditions. Certain other diagnoses can be difficult to make from plain radiographs, such as incomplete fracture/ossification. Although noninvasive techniques such as MRI or CT can help in this respect, arthroscopy may offer an alternative that is, in some ways, more practical in that treatment could readily be carried out under the same general anesthesia.

CARPUS/MANUS

Radiology

A **dorsopalmar** view is the single most useful radiograph but a **mediolateral** view will complement this and should certainly be taken if the carpus is suspected as the source of lameness. Mediolateral views taken with **one digit placed more extended** than the others may help and **oblique** or **stressed** views (extended/flexed mediolateral or abducted/adducted dorsopalmar) may be useful but are most often required for evaluation of instability relating to trauma.

How reliable is radiography in making a diagnosis in common/well-described causes of nontraumatic lameness involving the carpus/manus?

Very Reliable

- Osteoarthritis
- Other degenerative conditions such as enthesiopathies
- Neoplasia involving joint or bone
- Metaphyseal osteopathy
- Growth deformity

Intermediate/Helpful

- Some foreign bodies
- Immune-mediated arthropathy

Unreliable

- Soft tissue neoplasia
- Some foreign bodies

Ultrasonography

Not utilized for diagnosis.

Magnetic Resonance Imaging

Not generally used but might be utilized for selected cases

Arthroscopy

Not utilized.

USEFUL RADIOLOGICAL VIEWS OF THE SHOULDER

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SUPINATED VIEW

The usefulness of the supinated mediolateral shoulder view was first confirmed in a study with 20 shoulders affected by osteochondritis dissecans (OCD). Radiological signs evaluated included subchondral defect with flattening of the caudal humeral head, a sclerotic margin surrounding that defect, presence of a cartilage flap (only visible if mineralized), presence of "joint mice" (only visible if mineralized, most commonly found in the caudal recess of the joint), and secondary degenerative joint disease, most often seen as osteophyte formation on the caudal borders of the glenoid and/or the humeral head. Mediolateral and supinated mediolateral radiographs were compared. The lesions were more easily detected in the supinated view. This is especially true when the typical OCD lesion is not located in the caudo-central area of the humeral head: In approximately one third of the cases, the lesion is situated in the caudo-medial region. In these patients, the standard view may show a normal outline of the humeral head if radiographic changes are still subtle. If the clinician still has a high index of suspicion that the disease may be present, the supinated view is indicated

VACUUM PHENOMENON OF THE SHOULDER

A number of cases of shoulder OCD may exhibit the so-called vacuum phenomenon, which refers to the appearance of gaseous collections in the articular space when the leg is being extended, creating an image resembling a negative arthrogram. This permits direct visualization of the articular cartilage, usually radiolucid. This change was noted in 20 of 100 radiographs of shoulders affected by osteochondrosis and never in 30 radiographically normal contralateral joints. The phenomenon is found in addition to other radiographic changes and so should be added to the list of other possible findings rather than being considered as a separate entity.

SHOULDER ARTHROGRAPHY

Arthrography is considered an important ancillary diagnostic tool to visualize radiolucid structures and relevant soft tissues of the shoulder. The status of the articular cartilage, the presence of joint mice, the presence of vertical fissures in the cartilage flap, filling defects of the biceps tendon sheath, or irregularities in the contour of the intertubercular groove can readily be diagnosed without having to resort to arthroscopy or advanced imaging techniques.

To perform arthrography, the animal is anesthetized or heavily sedated and the cranial aspect of the shoulder joint is clipped and surgically prepared. The site for insertion of a 20- to 22-gauge, 1.5-inch needle is approximately between the acromion and the major tubercle of the humerus, in a cranio-distal direccion. The needle is advanced until joint fluid is aspirated. The needle is held steady, and the syringe is changed to a diluted contrast agent solution. The hub of the needle is filled with solution to avoid air bubbles before the rest of the injection is made. The contrast (usually diatrizoate) is diluted approximately to a 25% with saline solution. The volume of contrast depends on the size of the dog and the area to be examined. For an average Labrador, 3 to 4 mL can be instilled into the joint to diagnose shoulder OCD, and 4 to 5 mL to visualize the intertubercular groove. The most helpful radiographic view is the mediolateral view with the shoulder in a neutral position.

Positive-contrast scapulohumeral arthrography is critical in the evaluation of shoulder problems, with a low rate of false-positive and false-negative results. The accuracy of shoulder arthrograms has been rated as high as 90%

SKYLINE VIEW OF THE INTERTUBERCULAR GROOVE

Direct visualization of the intertubecular groove is an important aid for diagnosis of bicipital tenosynovitis. The most frequent radiographic sign in both lateral and craniocaudal views is an irregularity in the outline. In chronic cases osteophyte formation and subchondral bone sclerosis can also be detected. All these changes not always are obvious and arthrography or arthroscopy is usually required to confirm the diagnosis.

To overcome this problem, a technique was developed to obtain an axial view of the groove. This view is obtained with the dog in dorsal recumbency, with the affected shoulder joint hyperflexed and the limb rotated externally approximately 30°. This view isolates the intertubercular groove, making it easy to identify subtle irregularities and biceps tendon mineralization. It also provides a better localization of some cases of mineralizations of the supraspinatus tendon in relation to the biceps tendon sheath. It can aid in the differentiation between loose joint mice and osteoarthritic spurs within the intertubercular groove from mineralization of the supraspinatus tendon.

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ADVANCED IMAGING AND DIAGNOSIS OF INTERVERTEBRAL DISK DISEASE

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THE SCIENCE BEHIND MAGNETIC RESONANCE IMAGING (MRI)

The nucleus of an atom must contain an uneven number of protons in order to be affected by a magnetic field. The simplest atom to contain an odd number of protons is hydrogen, which contains just one proton. Presently, all clinical applications of MRI utilize the hydrogen nucleus. Hydrogen protons are abundant in the body. When located in a random direction, each proton's magnetic field will cancel each other out. However, when a patient is placed in a magnetic field, the proton becomes orientated either parallel or anti-parallel to the magnetic field. Parallel creates a low energy state and anti-parallel creates a high-energy state. When stimulated by a pulsation of radiofrequency waves from a transmitter coil, the protons flip their orientation 90° and start to rotate or resonate at a characteristic frequency, the resonant frequency. The magnetic fields of the resonating protons induce a voltage in a receiver coil, producing a signal. Immediately after the pulse, the spin starts to move out of the transverse position and start rotating out of phase, causing the signal to decay. Because the hydrogen protons of various tissues in the body are held together differently, the rates of relaxation will be different and characteristic for that tissue. These differences can then be measured and exploited to provide tissue contrast to the image.

The unique advantage of MRI is the ability to image in different planes. These planes are defined by using the three-dimensional Cartesian coordinate system (x, y & z axes). Generally the operating factors controlling the appearance of a regular x-ray or CT (as well as ultrasound or nuclear medicine) are limited. With MRI, however, there are literally hundreds of ways to perform an exam. Depending on which pulse sequence is used, tissues will show up as black, white, and everything in between. For example, pure water such as CSF will appear black on the T1 image and white on the T2 image.

T1-WEIGHTED IMAGES

A radiofrequency (RF) is sent in and displaces the longitudinally aligned proton by 90 degrees in the transverse plane. When the RF pulse is turned off, the protons will want to straighten themselves in the longitudinal direction, where they were in the first place. The faster they return to their original position aligned with the main magnet, the stronger the signal and the brighter the visualized structure. It is crucial to measure the emitted signal early so as to differentiate it from those sent out by the various tissues as eventually the protons will all realign and show no differentiation. The sampling time is known as TR and to maximize T1 contrast one must use a short TR sampling time.

T2-WEIGHTED IMAGES

T2 contrast relates to transverse magnetization. In addition to the realignment in the longitudinal plane, turning off the RF signal results in what is called a "dephasing" in the transverse plane: ie, while in the transverse plane when the RF pulse was on, the protons were all resonating in phase. When the RF pulse was turned off they started to dephase at different rates. At this time, a follow-up 180° RF pulse is given which puts the dephasing protons back in phase. As time passes, these protons again become out of phase and the signal decreases. Tissues which have a long T2 remain in phase for a lengthy period of time and emit a stronger signal. Since all tissues are initially in phase, maximum T2 contrast can be obtained by delaying the sampling time in the transverse plane (a time designated as TE). Therefore, for maximum T2 contrast, a long TE is desired. If we negate the T1 contrast by using a long TR and then use a short TE to negate the T2 contrast, we will be left with an image that has a contrast only different in the proton density. This image is called the proton density image.

Tissues that have minimal hydrogen protons (air, bone, and calcification) will have no signal, and therefore will appear as a *signal void* or black. Because the spins of flowing blood do not stay in a slice long enough to be affected by the 180° pulse, they rapidly dephase and lose signal; thus they also appear as a signal void on spin echo images. Because fats have short T1 and T2 relaxation times (ie, they recover and decay quickly), they will appear relatively *hyperintense* with T1 weighting (short TR) and *hypointense* with T2 weighting (long TE) on spin echo images. Because pure liquids such as CSF have long relaxation times, they appear hyperintense with T2 weighting and hypointense with T1 weighting. Impure liquids such as the brain have intermediate intensity normally, but have a tendency to become more hyperintense with T2 weighting and either hypointense or isointense with T1 weighting when affected by inflammation or neoplasia.

CONTRAST ENHANCEMENT WITH MRI

On MR images, distribution of a paramagnetic agent (eg, gadolinium-DTPA (Gd-DTPA)) will appear bright on T1 because of its ability to shorten the relaxation time of nearby hydrogen protons. Contrast medium is used to identify blood vessels, to monitor blood flow, and to enhance lesions and normal tissue such as the parenchyma of organs. With brain imaging, contrast medium normally enhances the meninges and choroid plexus and the pituitary gland because their capillaries are fenestrated and permit passive diffusion of contrast medium into their interstitium. Contrast medium does not normally enter the brain parenchyma because of the blood–brain barrier. When this barrier breaks down, substantial leakage of proteinaceous plasma filtrate into the extracellular space of the brain from the diseased or damaged capillaries results in vasogenic edema. This edema migrates along the white matter fire tracts and usually does not enter the tightly integrated cortical gray matter. The abnormal signals from lesions can be differentiated from the vasogenic fluid that intially saturates the perilesional space by the process of contrast enhancement. On T1-weighted images, the Gd-enhanced lesion will appear hyperintense and may be surrounded by hypointense perilesional edema.

SPINAL MRI

The spatial resolution of MRI generally is not as good as CT for spinal imaging but the greater contrast resolution that is provided by MRI ensures great anatomic detail. This especially pertains to the structure of the disc and the spinal cord itself. The image sequencing used determines the appearance of the normal spine. With T1-weighted images (T1W), intervertebral disks are of nearly uniform medium signal intensity, slightly greater than that of the spinal cord. The spinal cord and nerve roots are isointense, with slightly less intensity than the disk. Epidural fat has a short T1 relaxation time and so is hyperintense, providing great contrast with the surrounding structures. Cortical bone of the vertebrae appears as a black shell in all imaging sequences owing to its relative lack of hydrogen. It is difficult to define the longitudinal and interarcuate ligaments except over the disk spaces.

On T2-weighted (T2W), normal intervertebral disks are characterized by a high-signal central area surrounded by a medium-signal area. This is due to the varying content of ground substance within the structure of the disk. The ground substance is composed of hyaluronic acid and glycosaminoglycans that have a strong negative charge and therefore attract and hold water. Epidural fat has medium signal intensity, considerably lower than that seen on T1W images. Heavily T2W images show an area of high signal intensity surrounding the spinal cord, creating a natural myelogram effect. As with the T1 images, cortical bone and the ligaments of the spine are of low signal intensity and cannot be resolved.

DISK DISEASE

MRI is becoming the imaging modality of choice for the evaluation of degenerative spinal disease in centers that have this facility. This is because MRI has a high sensitivity for the evaluation of disk degeneration. Most reports in veterinary medicine are limited to the study of LS disease in dogs. Disk degeneration is best seen on sagittal T2W images as partial or complete loss of the normal high signal within the nucleus pulposus and inner annular portions of the disk. This again is due to the variations in the content of ground substance in the disk (decreased in the dehydrated degenerative disk). The presence of a normal signal within a disk on T2W images can help rule out disk degeneration.

Anatomic detail is best seen on T1W images because of high signal-to-noise ratio and sharp contrast between high signal epidural fat. The intervertebral disk protrusion can be seen as a dorsal displacement of the disk into the spinal canal, loss of the normal shape of the disk and displacement of the epidural fat on sagittal images. The images can also define a lateralized disk by virtue of its occlusion of the intervertebral foramen and its subsequent affect on the periradicular fat. Transverse images can be helpful with the assessment of the degree of narrowing of the vertebral canal by permitting the visualization of the cross-sectional area of the vertebral canal.

T1W contrast medium such as gadolinium-DTPA has two major applications in the evaluation of degenerative spinal disease. Firstly, the differentiation of a lateral disk herniation from a nerve root tumor, the latter enhancing with contrast administration. This is only possible if the images are taken immediately after the contrast administration as the disk material will contrast enhance after time. Second, the use of contrast to differentiate recurrent disk herniation from scar formation at the site of a previous surgery has been described. A scar will typically enhance uniformly, whereas herniated disk material will not do this immediately.

VACCINATION 2008 – BUILDING THE PROTOCOL...IMPLEMENTING THE GUIDELINES

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Vaccination *Guidelines* for the cat were first published in 1998; canine *Guidelines* followed in 2003. By the end of 2006, both sets of *Guidelines* had been reviewed extensively, updated, and published. Today, the complete text of both the AAHA Canine Vaccine Guidelines (www.aahanet.org) and the AAFP Feline Vaccine Guidelines (www.aafponline.org) is available to the entire profession. Let there be no question...veterinarians continue to pay close attention to the numerous, sometimes controversial, presentations and publications that address how we should select and use vaccines in companion animal practice. Yet, whether or not you intend to implement any of the recommendations outlined, every clinician should at least read the *GUIDELINES*. These two publications serve as a critical resource for any veterinary practice engaged in administering vaccines to dogs and cats. The pace of change regarding vaccine technology along with new product introductions virtually mandates that veterinarians carefully assess the manner in which vaccines are selected and used.

Today there's simply no room for complacency with respect to developing a *rational vaccination protocol*. It's a fact—there are too many issues and too many new facts to ignore the changes impacting the selection and use of vaccine.

Perhaps the single most significant challenge regarding implementation of a vaccine protocol in practice today is the number of vaccines available today. At this writing, there are approximately 26 vaccine antigen types for the dog and 18 types for the cat; combined, there are over 150 proprietary (trade name) vaccines in the US! Just months after publication of the 2006 Feline Vaccination Guidelines, two new vaccines were licensed (VS Feline Calicivirus and Canine Malignant Melanoma-therapeutic vaccine); throughout 2008 it is reasonable to expect additional canine and feline vaccines will be licensed.

But it's not just the number of new vaccines that impact vaccination protocols used in practice, it's the frequency of vaccination, it's the duration of immunity of the various vaccines we use, it's the dramatic change occurring in vaccine technology and development, it's vaccine safety, it includes medical, legal, and ethical responsibilities and more.

The objective of this article is not to attempt defining standards for vaccinating dogs and cats, nor is it to recommend a universal vaccination protocol. Instead, the goal is to facilitate the efforts of individual clinicians in implementing a ***rational*** vaccination program, consistent with current body of knowledge.

BUILDING THE PROTOCOL

The concept of CORE and NON-CORE vaccines is valid and has direct application in veterinary medicine today. Simply stated, this means separating the vaccines currently in your refrigerator into two separate groups: those that every dog and every cat will receive (CORE) and those that the attending clinician decides are necessary (or NOT necessary) based on health risk assessment of the individual patient (NON-CORE). While this may not sound especially important, there is value in assuring that every person in the hospital, technicians as well as veterinarians, is aware of the CORE vaccines and can consistently communicate the same vaccine message to clientele. The series of four tables that follow represent a list the CORE vaccines for the dog and cat *and* current recommendations for incorporating these vaccines into a rational vaccination protocol.

Antibody Titers vs. Annual Vaccination

Current vaccination guidelines for the dog and cat recommend triennial administration of core vaccines rather than the conventional annual booster recommendation found on the package inserts of most products. Veterinarians seeking serologic evidence of sustained immunity to prior vaccination, along with client concerns over excessive vaccination practices, prompted an increase in requests from practices for antibody titers against selected canine and feline antigens. The widespread availability of "vaccine titers" has culminated in questions concerning indications for testing, interpretation of test results (POSITIVE vs. NEGATIVE), and the significance of using these tests as part of a patient's routine health care assessment. A recent issue of *Immunology Bulletin* addresses these key points.

WHAT DOES A TITER SIGNIFY?

When submitting serum from an individual patient to assess serologic response to vaccination, the Ab titer reported only indicates prior exposure to a particular antigen. It does not distinguish between natural exposure, vaccination, or (in puppies/kittens) maternally derived Ab, *nor does it represent confirmation of infection.*

It must not be assumed that a vaccine titer reported as POSITIVE is confirmation that the patient is resistant to infection. There is considerable variation in the significance of a POSITIVE titer result. For example, leptospirosis Ab titers are used diagnostically to assess prior and current exposure, but antibody titers do not correlate well with immunity or susceptibility. Cats having a POSITIVE titer to feline herpesvirus-1 or calicivirus are likely to experience minimal clinical disease following exposure, but are not resistant to infection and subsequent viral shedding.

On the other hand, a POSITIVE Ab titer to canine distemper or parvovirus and feline parvovirus (panleukopenia) generally correlates with protection against challenge. However, a POSITIVE Ab titer in an individual patient only reflects past immunity. The patient that is POSITIVE today may not be POSITIVE tomorrow.

Interpretation of a NEGATIVE titer is somewhat more complex. Antibody is subject to catabolism over time. The absence of a measurable Ab titer does not necessarily correlate with susceptibility. Immunologic "memory," in the form of B-lymphocytes and plasma cells can be called on for a rapid immunologic 'boost' in the event of subsequent exposure. This is particularly true for canine distemper and canine/feline parvovirus.

INDICATIONS FOR TESTING

Routine testing of dogs and cats for Ab titers to core vaccines is not generally recommended. While a POSITIVE titer likely correlates with protective immunity (canine distemper and canine/feline parvovirus), a NEGATIVE titer, a rare finding in previously vaccinated animals, does not necessarily define susceptibility.

Indications for testing are generally limited to the assessment of individual puppies and kittens for evidence of a response to the initial series of core vaccines. Serum can be submitted as early as 2 weeks following the last of vaccines in the series. Testing of puppies and kittens is reasonably limited to high risk groups (group housing environments, use of dog 'day-care' facilities, and frequenting dog parks). Today, there is no known breed-predisposed susceptibility to infection (eg, Rottweillers and parvovirus) that justifies routine Ab testing.

Antibody testing, in lieu of vaccination, is also indicated in patients with a prior history of having experienced a known or suspected adverse vaccine reaction. Likewise, patients having recovered from an immune-mediated disorder, eg, immune-mediated hemolytic anemia or thrombocytopenia, are reasonably subjected to antibody titers rather than booster vaccination. In the unlikely event a patient has a negative Ab titer, the decision to vaccinate or not is left to the discretion of the individual clinician. Rabies vaccination may not be an option in those States that do not recognize rabies vaccination waiver authority to veterinarians.

Routine use of serologic testing to assess immunity in the individual dog or cat carries significant limitations. Variation of test results reported by individual laboratories, the lack of uniform laboratory standards for performing titers, and the inability of these tests to reliably distinguish protected from susceptible patients requires the clinician to have a clear understanding of the meaning of an antibody titer in the individual patient.

VACCINE-ASSOCIATED SARCOMA (VAS) vs. ADJUVANT

The association between feline rabies and feline leukemia (FeLV) vaccination and tumorigenesis was established in 1993. Ironically, in 2001, the AVMA's Vaccine-Associated Feline Sarcoma Task Force published vaccination-cite recommendations for both FeLV and rabies vaccines: rabies RIGHT (rear leg); leukemia LEFT (rear leg) "as distally as feasible." The reason (not specifically stated in the guidance) was to facilitate tumor management through amputation of the affected leg in order to save the patient. This hardly seems a rational solution to the problem.

MITIGATING RISK

First...it's a Cat Thing!

VAS has been reported in humans and in dogs, but documented cases are exceptionally rare compared with the VAS prevalence recognized in cats. Yet it's not just vaccine. There are published reports documenting fibrosarcoma formation in cats subsequent to ocular trauma, repository drug administration, and nylon suture left in skin for an extended time. In addition, all cats do not have equal risk. Yet undefined genetic determinants are likely to play a role.

Second...it was 1985!

In 1985, the first feline leukemia vaccine (aluminum adjuvanted) was licensed in the US. Being the first FeLV vaccine to reach the market, widespread use followed. Also in 1985, sale of modified-live rabies vaccine in the US was withdrawn and replaced with killed, adjuvanted rabies vaccine. Then, in 1987, the State of Pennsylvania issued legislation that required, for the first time, all cats receive a rabies vaccine. It was in 1991 that the Pathology Laboratory at the University of Pennsylvania, School of Veterinary Medicine reported a significant increase in the number of fibrosarcomas in cats. They went on to note that these tumors were particularly aggressive, were occurring in younger, versus older, cats, and that the tumors occurred in a location where veterinarians commonly administer vaccine.

Third...the Science is Compelling

Several scientific studies published in the last 10 years support a link between adjuvant-induced inflammation and sarcoma formation in some cats. While it may never be possible to actually proved cause-and-effect, the evidence is compelling. For this reason, the AAFP Feline Vaccine Advisory Panel has recommended that veterinarians avoid the use, whenever feasible, of vaccines that are associated with inflammation. In effect, the Advisory Panel is recommending that veterinarians avoid the use of adjuvanted vaccine, when feasible.

Note: The presence or absence of adjuvant is NOT required on the product label. The only way to know if a feline vaccine is adjuvanted is to know whether or not the product contains a killed virus or bacterial antigen. All killed vaccines are adjuvanted. Modified live and recombinant feline vaccines are not adjuvanted.

"3-YEAR" VACCINES vs. TRIENNIAL VACCINATION RECOMMENDATIONS

Recommendations of the AAHA Canine Vaccine Task Force and the AAFP Feline Vaccine Advisory Panel include administration of core vaccines to adult dogs (distemper, parvovirus, adenovirus-2) and cats (panleukopenia, herpesvirus-1, calicivirus) triennially (every 3 years). These recommendations were based on data derived from recent challenge and serological studies involving vaccines that have been on the market for the past 6 years. While most vaccines have a minimum duration of immunity (the *maximum* is not known) of 5 to 7 years, the 3-year recommendation is regarded as a standard of care that does provide protection to dogs and cats in the face of natural challenge.

Subsequent to the publication of the AAHA and AAFP triennial vaccine guidelines, most vaccine manufacturers provided data on individual products that supported these recommendations. Vaccines labeled for 3-year administration were also released. It should be noted, however, that:

1. veterinarians are NOT required to vaccinate adult dogs and cats every 3 years; administration of *annual* boosters still represents a standard of care in veterinary medicine today…and,
2. furthermore, there is no legal or ethical mandate for veterinarians to use a vaccine licensed for administration every 3 years in order to comply with current published vaccine guidelines. All core vaccines (modified live and recombinant) are regarded as 3-year vaccines, regardless of the manufacturer.

Any implication that a "3-year vaccine" *must* be used when adhering to current vaccination recommendations is wrong…and misrepresents the intent of the 2006 AAHA Canine Vaccine Guidelines.

ADDITIONAL READING

1. 2006 Canine Vaccine Guidelines and Recommendations. American Animal Hospital Association (AAHA) Canine Vaccine Task Force: (the complete Report, including Supporting Literature, is available at www.aahanet.org).
2. 2006 Report of the American Association of Feline Practitioners (AAFP) Feline Vaccine Advisory Panel. *J Am Vet Med Assoc* 2006; 229(9):1405-1441. The entire report and references are available at: www.aafponline.net
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Table 1. CORE Canine Vaccines and Recommendations for Administration (based on the 2006 Report of the AAHA Canine Vaccine Task Force)

CORE Vaccines	Primary Puppy Series (≤ 16 weeks)	Primary Adult Series (> 16 weeks)	Booster Interval
Distemper Recombinant, or Modified-Live **Parvovirus** Modified-Live **Adenovirus**-2 Modified-Live (SQ injection)	Administer 1 dose at 6–8 weeks of age, then, Every 3 to 4 weeks until 15–16 weeks of age. (Initial series includes 3 to 4 doses depending on age at the time of first vaccine)	Administer 2 doses 3 to 4 weeks apart.	Administer 1 dose one year following completion of the initial series; then Every 3 years thereafter.
Rabies Killed, 1–Year Killed, 3–Year (SQ injection)	Administer 1 dose at 12 to 16 weeks of age.	Administer 1 dose	Administer 1 dose one year following administration of the first dose, then Every 3 years thereafter.

NOTE: Requirements for canine rabies vaccination are established by State and/or local statutes and may differ from the recommendations listed above.

Recombinant Canine Distemper Virus Vaccine: An independent study (U of Wisconsin,2006) has shown that the recombinant Canine Distemper Virus (rCDV) vaccine was able to protect puppies against the consequences of infection using only 1 dose administered at 8 weeks of age. This heightened immunity results from the inability of maternal antibody to recognize and interfere with the recombinant CDV vaccine. Today, the AAHA Canine Vaccine Task Force recommends administration of this vaccine to puppies as young as 3 weeks old in the face of CDV outbreak (see Shelter Guidelines)

An additional vaccine challenge study (2007) designed to assess the duration of immunity of the recombinant CDV vaccine demonstrated a minimum duration of immunity that exceeds 3 years. Hence veterinarians electing to implement triennial vaccination of core canine vaccines can use either recombinant or Modified Live Virus vaccine for canine distemper. Current AAHA Guidelines have been amended to reflect these data.

Table 2. NON-CORE Canine Vaccines and Recommendations for Administration (Based on the Report of the 2006 AAHA Canine Vaccine Task Force)

NON-CORE (optional) Vaccines	Primary Puppy Series (≤ 16 weeks)	Primary Adult Series (> 16 weeks)	Booster Interval
***Bordetella bronchiseptica* + Parainfluenza** Avirulent-Live (intranasal administration ONLY)	A single dose is recommended by the manufacturers and may be given as early as 3–4 weeks of age. 2 doses, 2–4 weeks apart are recommended. May be given as early as 3–4 weeks of age.	A single dose.	Annually; animals in a high risk/exposure environment may benefit from a booster if longer than 6 months since the previous dose.
Bordetella bronchiseptica Killed, or Antigen Extract (SQ administration)	Administer 2 doses, 2 to 4 weeks apart beginning as early as 8 weeks of age.	Administer 2 doses, 2–4 weeks apart.	Annually; animals in a high risk/exposure environment may benefit from a booster if longer than 6 months since the previous dose.
Leptospirosis (serovars: canicola, icterohemmorhagiae, pomona, grippotyphosa) Various 2-way and 4-way combinations are available. Killed bacterin (SQ administration)	Administer 2 doses, 2 to 4 weeks apart beginning as early as 12 weeks of age. (Vaccination of dogs less than 12 weeks of age is generally not recommended)	Administer 2 doses, 2–4 weeks apart.	Annual booster is recommended for dogs with a defined risk of exposure. Vaccination is *not* recommended for all dogs. Exposure risk should be considered prior to recommending.
Lyme borreliosis Recombinant, or Killed bacterin (SQ administration)	Administer 2 doses, 2–4 weeks apart beginning as early as 12 weeks of age.	Administer 2 doses, 2–4 weeks apart.	Annual booster is recommended for dogs with a defined risk of exposure. Vaccination is not recommended for all dogs.
Crotalus atrox (Western Diamondback Rattlesnake vaccine) Toxoid (SQ administration)	Recommendations vary depending on size of the dog and risk of exposure. See Manufacturer's Recommendations.	Recommendations vary depending on size of the dog and risk of exposure. See Manufacturer's Recommendations.	Not Stipulated. Duration of immunity studies have not been conducted.
***Porpyhromonas* spp.** Killed bacterin (SQ administration)	Administer 2 doses, 3 weeks apart beginning as early as 7 weeks of age (manufacturer recommendation)	Administer 2 doses, 3 weeks apart.	Not Stipulated. Duration of immunity studies have not been conducted.

NOTE: Although vaccines licensed by the USDA are currently available in the United States, routine vaccination of dogs against coronavirus and *Giardia lamblia* is NOT recommended.

Table 3. CORE Feline Vaccines and Recommendations for Administration
(Based on the 2006 Report of the AAFP Feline Vaccine Advisory Group)

CORE Vaccines	Primary Kitten Series ($\leq$ 16 weeks)	Primary Adult Series (> 16 weeks)	Booster Interval
Parvovirus (Panleukopenia) **Herpesvirus-1 and Calicivirus** Modified-Live (non-adjuvanted) or… Killed (adjuvanted) (SQ or intranasal administration)	Administer 1 dose as early as 6 weeks of age, then Every 3–4 weeks until 16 weeks of age	Administer 2 doses, 3–4 weeks apart	Administer 1 dose one year following completion of the initial series; then every 3 years thereafter. Note: Annual booster of cats against FHV-1 and FCV may be recommended in cats housed in high risk environments.
Rabies Recombinant (non-adjuvanted) (SQ injection)	Administer 1 dose at 12–16 weeks of age.	Administer 1 dose	Annually
Rabies Killed, 1–Year Killed, 3–Year (adjuvanted) (SQ injection)	Administer 1 dose at 12–16 weeks of age.	Administer 1 dose	Administer 1 dose one year following administration of the first dose, then every 3 years thereafter.

NOTE: Requirements for feline rabies vaccination are established by State and/or local statutes and may differ from the recommendations listed above.

Table 4. NON-CORE Feline Vaccines and Recommendations for Administration (based on the 2006 Report of the AAFP Feline Vaccine Advisory Group)

NON-CORE (optional) Vaccines	**Primary Kitten Series (≤ 16 weeks)**	**Primary Adult Series (> 16 weeks)**	**Booster Interval**
Feline Leukemia Recombinant (non-adjuvanted) (Transdermal administration ONLY)	Administer 2 doses, 3 to 4 weeks apart beginning as early as 12 weeks of age.	Administer 2 doses, 3 to 4 weeks apart.	Annual booster; booster vaccination is *not* recommended for all cats. Exposure risk should be considered prior to recommending.
Feline Leukemia Killed (adjuvanted) (SQ administration)	Administer 2 doses, 3 to 4 weeks apart beginning as early as 12 weeks of age.	Administer 2 doses, 3 to 4 weeks apart.	Annual booster; booster vaccination is *not* recommended for all cats. Exposure risk should be considered prior to recommending.
Chlamydophila felis Avirulent Live (non-adjuvanted) (SQ administration)	Administer 2 doses, 3 to 4 weeks apart beginning as early as 12 weeks of age.	Administer 2 doses, 3 to 4 weeks apart.	Annual booster; booster vaccination is *not* recommended for all cats. Exposure risk should be considered prior to recommending.
Chlamydophila felis Killed (adjuvanted) (SQ administration)	Administer 2 doses, 3 to 4 weeks apart beginning as early as 12 weeks of age.	Administer 2 doses, 3 to 4 weeks apart.	Annual booster; booster vaccination is *not* recommended for all cats. Exposure risk should be considered prior to recommending.
Feline Immunodeficiency Virus Killed (adjuvanted) (SQ administration)	Administration of 3 initial doses is required. Beginning as early as 8 weeks of age, administer 2 additional doses 2 to 3 weeks apart.	Administration of 3 initial doses is required. Each dose should be administered 2 to 3 weeks apart.	Annual booster; vaccination is *not* recommended for all cats. Exposure risk should be considered. NOTE: A single dose of FIV vaccine will cause a false-positive test result on all commercial FIV tests.
Bordetella bronchiseptica Avirulent Live (non-adjuvanted) (Intranasal ONLY)	Administer a single dose as early as 8 weeks of age.	Administer a single dose	Annually, but only in cats with established risk of exposure
Virulent Systemic Calicivirus Killed (adjuvanted) (SQ administration)	Administer 2 doses, 3 to 4 weeks apart beginning as early as 12 weeks of age	Administer 2 doses, 3 to 4 weeks apart.	Duration of immunity is not known. Annual booster is recommended by the manufacturer.

NOTE: Although vaccines licensed by the USDA are currently available in the United States, vaccination of cats against feline coronavirus (FIP) and *Giardia lamblia* is NOT recommended.

BORDETELLA BRONCHISEPTICA VACCINATION: SQ OR IN?

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Closely related to *Bordetella pertussis*, the cause of "whooping cough" in humans, *Bordetella bronchiseptica* is a gram-negative, aerobic coccobacillus particularly well adapted to colonize the ciliated respiratory epithelium of dogs and cats. Today, this organism is regarded as a principal (although not the only) etiologic agent of canine infectious tracheobronchitis (ITB). In the clinical setting, however, *B. bronchiseptica* infection should not be regarded as synonymous with ITB. Dogs infected with canine parainfluenza virus (CPiV) or canine adenovirus-2 (CAV-2) are expected to experience more severe respiratory disease when co-infected with *B. bronchiseptica* than with any these agents alone. Canine bordetellosis—that is, *B. bronchiseptica* infection—in the absence of either CPiV or CAV-2, is known to occur and can be associated with acute, fatal pneumonia, particularly in young dogs.

One particularly important point regarding *B. bronchiseptica* is the fact that bacteria are principally transmitted through aerosolization of respiratory secretions. Direct transmission through contaminated dishware, human hands, and other fomites is also reported. Because *B. bronchiseptica* possesses several intrinsic mechanisms for evading host defenses, it is recognized for its role as a significant complicating factor in dogs with multiple-agent respiratory infections. The fact that outbreaks of canine ITB are common, despite widespread use of topical and parenteral vaccines in dogs for over 20 years, highlights the fact that current vaccines are more effective in preventing clinical illness than they are in preventing infection. Our understanding of the role that *B. bronchiseptica* has in feline respiratory disease is only beginning to undergo scientific scrutiny.

VACCINATION

Vaccination against the predominant agents involved in canine ITB (especially *B. bronchiseptica* and parainfluenza virus) has proven to be an important component of ITB prevention, particularly in high-density environments, such as shelters, kennels, and rescue groups. Today, several commercially licensed canine vaccines against many of the pathogens associated with canine ITB (*B. bronchiseptica*, CAV-2, CPiV, and canine distemper virus) are available. At this time, there is only one vaccine licensed for protection against feline *B. bronchiseptica* infection. Canine vaccines are available for both topical (avirulent-live bacteria for intranasal use only) as well as parenteral (cellular antigen extract) administration; the feline *B. bronchiseptica* vaccine is approved for topical (intranasal) administration only. All intranasal vaccines approved for use in dogs also include modified live parainfluenza virus. Some products also contain modified live canine adenovirus-2.

The efficacy of vaccination administered by either the topical or the intranasal route is well documented. Regardless of the route of administration, vaccinated dogs experience substantially less coughing when compared with control dogs following challenge. Vaccination is not expected to completely eliminate the risk of infection and development of subclinical to mild infection following exposure.

Previous serologic (non-challenge) studies indicated that the use of intranasal vaccine to booster previously vaccinated or exposed dogs failed to induce a significant antibody response. It was suggested that only parenteral vaccination could be used effectively in adult dogs to boost immunity. However, a recent study has demonstrated significant protection in induced in adult dogs following intranasal vaccination. Of particular importance, these studies demonstrated that intranasal vaccination prevented shedding of bacteria following exposure; parenterally administered vaccines were not able to prevent shedding.

Also in support of intranasal vaccination is the fact that parainfluenza vaccine may actually be more efficacious in preventing clinical signs compared with parenterally administered vaccine. Hence, the combination *B. bronchiseptica* + Parainfluenza combination vaccine for intranasal administration is an excellent choice. Dogs that become aggressive during attempts to administer intranasal vaccine should be vaccinated by the parenteral route.

The onset of immunity following booster intranasal vaccination of dogs has been demonstrated to be as early as 3 days. In clinical practice, however, a 5-day post vaccination interval is recommended. The onset of immunity following vaccination with the parenteral (cellular antigen extract) has not been published.

No studies are available comparing the duration of immunity subsequent to parenteral versus intranasal vaccination. Intranasal vaccines have been demonstrated to prevent clinical signs following challenge for periods of 12 to 14 months post-vaccination. Annual vaccination is appropriate for dogs with low to moderate risk of exposure. It is the author's recommendation that dogs housed in a high risk environment may benefit from vaccination every 6 months.

Recommendations outlined by the American Association of Feline Practitioners indicate that *B. bronchiseptica* vaccination in not required in all cats. Use of the vaccine is generally limited to cluster households and shelters where *B. bronchiseptica* is known to be associated with lower respiratory infection in cats. As occurs in dogs, transient post-vaccinal sneezing or cough is expected in some cats within 24-hours post-vaccination.

FURTHER READING

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TREATING INFECTIONS IN IMMUNOCOMPROMISED PATIENTS

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Veterinarians are often required to treat infections in animals with concurrent immunocompromise. There are a variety of both congenital and acquired reasons for immunocompromise. While congenital immunodeficiency syndromes are rare (eg, neutrophil defects, IgA deficiency), acquired immunodeficiency is encountered commonly as a result of infection (eg, feline leukemia virus infection, feline immunodeficiency virus, canine parvovirus) or as a consequence of concurrent metabolic disease (eg, uremia, diabetes mellitus). Almost as commonly, veterinarians induce immune suppression (ie, immunocompromise) iatrogenically during the course of treatment for immune-mediated, neoplastic, and inflammatory disease. In addition, any time a veterinarian breaches a physical barrier (eg, intravenous or urinary catheter insertion, endotracheal intubation) they compromise normal protective mechanisms. Any compromise in immune function can increase the risk of secondary or opportunistic infections, while simultaneously making it more difficult to eradicate those infections. Despite the difficulty, it is still possible to effectively treat infectious complications in the immunocompromised host.

SPECIFIC IMMUNOLOGIC PROTECTION

The immune system is a tremendously complicated network of interconnected responses. Because of its crucial role in prevention and response to infection, there is much overlap in protective function. However, each component of the immune response is best suited to deal with specific kinds of infection. For this reason, all immunocompromise is *not* created equal. Different sorts of infection are to be expected and different therapeutic considerations may apply depending on the type of immunocompromise The immune system can be roughly divided into two major divisions: innate immunity and acquired immunity.

Innate immunity possesses neither specificity nor memory. Essentially, innate immunity is equipped to deal with a variety of pathogens immediately on initial exposure but response to that pathogen does not improve on subsequent exposure. Innate immunity includes phagocytic cell function (eg, neutrophils), complement, and chemicals such as defensins. Although involved to some degree with the response to any infection, innate immunity is most crucial in response to bacterial and fungal pathogens.

Acquired immunity possesses both specificity and memory. Some period of time is required after initial exposure to a pathogen to “gear up” acquired immunity, but on subsequent exposures the immune system will “remember” the pathogen and will be able to deal with it more rapidly and efficiently. There are two subcomponents to acquired immunity: cell-mediated immunity (CMI) and humoral immunity. CMI is carried out by effector cells such as cytotoxic T lymphocytes, while the effector cell of humor immunity is the differentiated B lymphocyte, or plasma cell. Plasma cells generate soluble antibodies specific for a given pathogen. Humoral immunity is crucial for immune exclusion at mucosal sites (eg, prevention of infection in the respiratory airways) while CMI is crucial for response to intracellular pathogens. Both CMI and humoral immunity are involved in prevention of viral disease, with difference in degree of importance depending on the specific pathogen in question.

Immunocompromise can affect any or all of the components of immunity. The type of infection most likely to occur in an immunocompromised individual depends in large part on the portion of the immune system that has been injured. The type of infection may also be related only indirectly to failed immunity, but to other aberrations in physical, chemical or mechanical defenses. For instance, animals with diabetes mellitus are susceptible to urinary tract infection not only as a result of impaired phagocytic cell function, but also as a result of a dilute urine containing glucose which offers greater opportunity for bacterial growth. Similarly, glucocorticoids impair immunologic function, but they also predispose to urinary tract infection by causing production of dilute urine, and distension of the bladder wall.

RECOGNITION OF INFECTION

Recognition of infection in immunocompromised patients can be difficult. Often, clinical signs such as fever, lethargy, anorexia, pain, or others are attributed to the underlying disease condition (eg, neoplasia) rather than to infection. Similarly, classic laboratory indicators of infection such as leukocytosis may be mistakenly attributed to underlying inflammatory or neoplastic disease or to a steroid leukogram when corticosteroids are administered. To add to the difficulty of recognizing infection, immunosuppressive drugs may prevent typical expressions of infection such as fever. Corticosteroids are potentially the most commonly used immunosuppressive drug. Because corticosteroids are potent inhibitors of arachidonic acid metabolism, they inhibit formation of prostaglandins crucial to the febrile response. For this reason, fever may be absent or mild in animals with severe infection who are concurrently receiving corticosteroids. Recognition of urinary tract infections is particularly difficult. Many such infections are asymptomatic when associated with corticosteroid therapy, diabetes, hyperadrenocorticism, or other condition than may have compromised defenses of the lower urinary tract. In addition, WBC or bacteria may not be noted in dilute urine specimens.

TREATING INFECTION IN THE IMMUNOCOMPROMISED HOST

Fever in a neutropenic patient constitutes a medical emergency, but any immunocompromised patient with systemic signs of infection should be treated promptly and aggressively. Treating infections in immunocompromised animals presents a special challenge. Because of the patient's incompetent immune system, the correct selection of antimicrobial drugs and the appropriate dosing regimen is especially important. If fever and neutropenia are present, antibiotic therapy should be started promptly.

The use of prophylactic antibiotics in neutropenic patients without evidence of infection is likely warranted in at least some cases. In human medicine, a neutropenia < 500 cells/µL is the single most important risk factor for infection. Although specific studies addressing the issue have not been published, in veterinary patients a neutropenia of < 1,000 cells/µL is generally cited as an important threshold at which risk of infection increases and therefore antibiotic administration should be considered. If neutropenia is not severe (ie, >2000 cells/µL), and signs of infection are not present, antimicrobial administration is discouraged to minimize the risk of emergence of resistant bacteria and altered intestinal flora. Owners should be taught how to take their pet's rectal temperature daily and to call the veterinarian if pyrexia develops, in which case the animal is treated as neutropenic and febrile.

Treatment Guidelines

There have been no large comparative studies investigating effects of different antimicrobial regimens in immunosuppressed pets; therefore we rely on clinical evidence from human medicine. The clinician will need to consider whether drug combinations or monotherapy should be used, as well as the activity of drugs against specific pathogens. Resistant bacteria can be retained among an animal's flora long after drug therapy has been discontinued, so prior antibiotic exposure and the risk of bacterial resistance must also be considered. Generally, antimicrobials with "cidal" activity should be chosen in patients with immunocompromise in place of antimicrobials with "static" activity.

The Stable Immunocompromised Patient

Details of management of the stable immunocompromised patient with suspected infection depends on the type of infection and the underlying disease process. If immunocompromise results from iatrogenic treatments, these should be temporarily withheld if this is safely possible. Ideally, antimicrobial therapy (which often begins broadly) should be focused when a specific pathogen is identified. Culture and sensitivity from likely sites of infection should be obtained whenever possible prior to initiation of antimicrobial therapy. At a minimum, urine culture is usually warranted. When neutropenic or otherwise compromised animals with evidence of infection do not require fluid support or other treatments best administered in-hospital, oral antimicrobial administration and outpatient treatment has several advantages, just as it does in human medicine. A combination of oral antimicrobials such as fluoroquinolones (eg, enrofloxacin, marbofloxacin, orbifloxacin, and difloxacin) with a beta-lactam such as ampicillin-clavulanate (eg, Clavamox) can provide a fairly wide spectrum of coverage while avoiding the need for invasive catheter placement, causing less stress to the patient, reducing costs of hospitalization, and decreasing the risk of exposure to nosocomial pathogens. When treatment with antibiotics is initiated in the immunocompromised patient, the duration of treatment will vary depending on individual circumstances and risk factors. In the case of a neutropenic, febrile patient, one should administer antibiotics for 5 to 7 days after the temperature has returned to normal and neutrophil counts are at least >1,000 cells/µL.

If fever persists after empiric antibiotic treatment and diagnostic tests have failed to identify a specific pathogen, consider the addition of other drugs that broaden the spectrum. Regimens to consider adding to the therapy may depend on the patient's presentation, region of the country, and clinical history. These drugs may include doxycycline for a suspected tick-borne pathogen; clindamycin or metronidazole for a suspected anaerobic infection; or an antifungal drug (eg, fluconazole or itraconazole). Treatment of suspected Bartonella infection should include combination therapy with doxycycline-azithromycin or doxycycline-rifampin. Although better to err on the side of caution and initiate antimicrobial therapy, it must also be remembered that there are many non-bacterial, non-fungal causes of fever which will not respond to any antimicrobial regimen. For example, catheter associated phlebitis may cause fever that is best addressed by removing the catheter.

The Critical Immunocompromised Patient

If the infection is severe and potentially life-threatening an indwelling catheter is placed aseptically and IV fluids are administered as required. Injectable antimicrobials should be used in critically ill hospitalized patients with sepsis. Immunosuppressive drugs should ideally be discontinued until the patient is stabilized; this is certainly true of chemotherapeutic agents which may induce neutropenia. If the patient has been receiving corticosteroids, the adrenal response may be suppressed and the patient may have relative adrenal insufficiency. Although protocols have not been tested in veterinary patients, supplementation with physiologic or antiinflammatory doses of corticosteroids may be considered in these animals.

As with stable animals believed to be septicemic, specific evidence of the type of infection should be sought. Urinalysis and urine culture are indicated in addition to CBC and serum biochemical tests (eg, electrolytes, blood glucose, blood urea nitrogen concentrations). Two to three replicates of aseptically collected blood can be obtained at 30-minute intervals for aerobic and anaerobic bacterial cultures and antibiotic susceptibility tests. Empirical antimicrobial therapy may be initiated before the test results become available (which may take days). Reasonable empiric choices in these critical patients include:

- Aminoglycoside + Cephalosporin
- Aminoglycoside + Ampicillin-Sulbactam
- Aminoglycoside + Ticarcillin
- Fluoroquinolone + Clindamycin
- Fluoroquinolone + Ampicillin-Sulbactam
- Monotherapy with a Penem

It should be noted that gentamicin is associated with more resistance than other aminoglycosides and amikacin should be used as the aminoglycoside of choice if there is a possibility of resistance. If the animal shows improvement in the first 48 to 72 hours and does not require other treatments, it can be returned to the wards or sent home on oral antimicrobial therapy. Oral therapy may include a fluoroquinolone, fluoroquinolone + amoxicillin-clavulanate, fluoroquinolone + clindamycin, cefpodoxime proxetil, or trimethoprim-sulfonamide. As described previously, doxycycline or other drugs may be considered in some circumstances.

Urinary Tract Infection

UTI represents a common infection in immunocompromised patients, including patients with diabetes mellitus and those receiving corticosteroid drugs. As mentioned, these secondary UTI are often occult. Clinical signs may be minimal or may be attributed to underlying disease or drug therapy, and WBC and bacteria may be found in very minimal concentration in dilute urine. Treatment of complicated UTI must be based on urine culture and sensitivity, and even with this information it can be very difficult to eradicate infection. After initiating antimicrobial therapy, follow-up urine culture should be obtained after ~1 week to be sure of antimicrobial efficacy in vivo. Culture should be repeated ~1 week after antibiotics are discontinued, and again several weeks later if immunocompromise continues. For frequent recurrent UTI, once acute infection is resolved urinary antiseptics or daily antimicrobial administration may be useful to prevent re-infection. However, it should also be noted that it may not be necessary to eradicate bacteria altogether as long as the animal remains asymptomatic (including absence of calculi or renal pelvic dilation). In such cases, a wait and watch approach may be most useful.

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CONSIDERATIONS IN THE TREATMENT OF THE IMMUNOCOMPROMISED ANIMAL

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The treatment of the immunocompromised animal is one of the most challenging responsibilities confronting a clinician because not only does he/she have to be concerned about the seriousness of the underlying disease, but there is sometimes even greater concern for the life-threatening complications that can result from secondary infections. The impact of the secondary infection will depend on a variety of factors such as age, innate immunity and the degree of immunocompetence, primary underlying disease, co-existing congenital or familial immunodeficiency states, and the use of drugs that can further compromise the immune system. This article will cover the more common causes of immunosuppression and the pathologic complications that the clinician can encounter in everyday practice.

TREATMENT CONCERNS FOR THE CANCER PATIENT

Oncology patients are can have compromised immunity for several reasons including the cause of the cancer itself, if caused by retroviruses, the debilitation, acquired disorders of antibody production and cell-mediated immunity caused by the cancer, and the drugs used to treat the cancer. Only the latter cause will be covered in this section. Many of the cytotoxic drugs inhibit cell division, and when this occurs the B and T cells are often times destroyed thus impairing the body's ability to produce antibodies and to allow for cell-mediated immune protection. This can predispose the patient to overwhelming infection.

The alkylating agents are particularly prone to causing immune compromise because of their affinity for destroying rapidly dividing cells thus destroying the B- and T-cell response. These effects on the immune system are made even worse by cyclophosphamide's ability to suppress the bone marrow and cause neutropenia that heightens the patient's predisposition that much more to bacterial infection. The clinical danger point occurs when the neutrophil count is less than 1.5 x 10^3 cells/microliter. Whenever a drug such as this is used a battle of survival occurs between the beneficial effects of the drug versus its adverse effects plus the possible drug resistance of the tumor.

The purine analogs can similarly compromise the patient. The commonly used purine analog is azathioprine. It too destroys proliferating lymphocytes which can adversely affect the primary and secondary immune response. Azathioprine has antiinflammatory effects that can suppress macrophage activity and it suppresses both B and T cells equally. Its major adverse effect is bone marrow suppression with predilection for leukocyte production.

It is easy to see why the cancer patient can become a victim of the drugs that are used to treat its primary disease. Their immune system will be further compromised by the concomitant use of other immunosuppressive agents such as glucocorticoids and any devastating effect of myelophthistic tumor behavior. It is therefore essential that strict antiseptic techniques be used in all cancer patients that show evidence of immunocompromise.

Some tumors such as lymphosarcoma and multiple myeloma can cause acquired disorders of antibody production. This is more likely to happen when the tumor cells produce a paraprotein causing increased globulin production but simultaneously interfering with the patient's normal antibody response. Certain bacteria such as staphylococci and streptococci can take advantage of this situation and cause a variety of infections and bacteremia. Splenectomy can further compromise the patient.

Certain cancers and immunosuppressive drugs such as cyclosporine can interfere with cell-mediated immunity thus compromising the host defense system against some facultative and obligate intracellular parasites. Infections such as those caused by Mycobacterium and Candida can have disastrous consequences for the patient.

There are neoplastic disorders that can cause neutropenia even before any cytotoxic drugs are given to the patient. It is amongst the most important risk factors for serious infection in the immunocompromised host. As the neutrophil count declines from 1500 to less than 500 cells/microliter, an exponential increase occurs in the severity and the frequency of infections. This can be seen in myelophthisic disease caused by spread of the cancer to the bone marrow. Myelophthisis can occur with both lymphosarcoma and carcinoma types of neoplasia. The neutropenia is usually accompanied by an anemia and/or thrombocytopenia when this process occurs. The neutropenia is a common predisposing cause of sepsis.

Clinically the hallmark signs of sepsis are the sudden onset of weakness, mental depression, and anorexia. The clinician should immediately respond to these signs by thoroughly examining the animal and looking for any signs of inflammation along catheter sites. There should be a critical review of the treatment, and the collection of specimens of blood and urine for bacterial isolation and sensitivity. It behooves the clinician to treat the patient with broad-spectrum bactericidal antibiotics because neutropenic animals are predisposed to infection. Empirical antibiotic treatment is indicated in the febrile granulocytopenic patient because most of them will have an underlying infection. Selection of two drugs with activity against gram-negative enteric bacilli is common practice. Others might prefer to use a single drug such as imipenem with broad-spectrum cover.

When the neutrophil count is < 500 cells per microliter, treatment with granulocyte colony stimulating factor (GCSF) is indicated because of the seriousness of this particular situation. GCSF is a hematopoietic agent that acts as a cytokine in the bone marrow where it increases the proliferation, differentiation, and activation of progenitor cells in the neutrophil line. It is derived from human DNA and can therefore be accompanied by host antibody formation thus negating its benefits. The antibodies can cause severe neutropenia. It is administered subcutaneously to dogs and cats at a dose ranging from 1–5 micrograms/kg SQ daily for no more than 5 days.

Fungal infection can also be a secondary complicating factor and body fluids or tissue samples should be obtained for immediate cytological identification because of the long delay that accompanies fungal isolation and sensitivities. Any life-threatening systemic mycotic disease will often require the use of amphotericin B treatment.

TREATMENT CONCERNS FOR THE PATIENT WITH IMMUNE-MEDIATED DISEASE

The main clinical disorders in this category include immune hemolytic anemia, immune thrombocytopenia, and immune polyarthropathy. Others that will require immunosuppression include several dermatologic disorders, two of which include pemphigus vulgaris and nodular panniculitis; sterile meningitis; and various immune pulmonary and gastrointestinal disorders. Most of these conditions utilize glucocorticoids as the initial and primary drug of choice and most are started on immunosuppressive dosages prednisone ranging from 1–2 mg/kg given twice daily. The effects of such high doses of glucocorticoids on the immune system are substantial with effects involving various components of the immune system. The effects on neutrophils include decreases in chemotaxis and margination and impaired phagocytosis and bacterial killing thus predisposing the patient to infections that can involve many body tissues.

The effects of glucocorticoids on macrophages result in impaired chemotaxis, phagocytosis and bactericidal activity. Macrophages will also have decreased interleukin-1 production and antigen processing which will further the animal's predisposition to infection.

Glucocorticoids will cause depressed lymphocyte proliferation, depressed T-cell responses, impaired T-cell cytotoxicity, depressed interleukin-2 production and depressed lymphokine production. There is also a minimal decrease in immunoglobulin production.

The patient being treated with high doses of glucocorticoids will be further predisposed to infection if other cytotoxic or immune suppressive drugs are used simultaneously. The types of infections are diverse with bacterial infections being the most common followed by fungal infections. The usual inflammatory signs of infection might even be absent because of the anti-inflammatory effects of the glucocorticoid drugs. Furthermore, any mature leukocytosis might be due to the effects of the primary autoimmune disease or the glucocorticoid drug itself. The presence of immature neutrophils is suggestive of infection, but it can also occur with immune-hemolytic anemia without infection. Therefore, it behooves the clinician to take proactive action against infection by doing routine urinalysis and intravenous cannula assessment periodically during the animal's hospitalization. Any suspicious site of catheter contamination requires its immediate removal using sterile technique for submission to the microbiology laboratory for culture and sensitivity. The use of indwelling urinary catheters can pose a particular infection risk in these patients and should best be avoided unless conditions find it absolutely necessary.

TREATMENT FOR PATIENTS WITH UNDERLYING DISEASES THAT RENDER THEM IMMUNOSUPPRESSED

Many disorders can cause immunocompromise. Generally, this can accompany many infectious diseases, various neoplastic diseases, and even endocrinologic disorders. The immunocompromise of the animal with hypercortisolism is due to the supraphysiologic blood levels of cortisol. The adverse immunological effects of elevated levels of glucocorticoid hormones have already been described in the preceding section. The urinary tract and the skin are common sites of secondary bacterial infections in the dog with Cushing's disease/syndrome, and any evidence of such complications should be vigorously pursued with bacterial isolation and culture followed by treatment with the appropriate antimicrobial drug. Any indwelling catheter sites in such patients should be closely monitored for any signs of inflammation. Such occurrences should be accompanied by prompt catheter removal along with culture and sensitivity. Lower urinary tract infections in patients with hyperadrenocorticism can ascend to the kidney to cause pyelonephritis. Some patients will show minimal clinical signs of infection because of the anti-inflammatory effects of cortisol. The lowered resistance to infection is due to glucocorticoid-induced inhibition of neutrophil and macrophage migration to the areas of infection. Suspicion for pyelonephritis in the Cushing's patient should occur when there is a recurring urinary tract infection based on the appearance of pyuria and bacteria on the urine sediment examination. Diagnostic imaging such as ultrasonograms will greatly help identify the source of the infection. Medical management calls for microbial identification and antibiotic sensitivity testing which is then followed by a protracted course (4–6 weeks minimum) of antibiotic treatment.

Diabetes mellitus can alter the body's immune defenses therefore rendering the patient predisposed to infection. The reasons for this have not been completely explained but can involve abnormalities with cell-mediated immunity and abnormal phagocyte function as well as poor blood supply to various body tissues because of diabetic vascular disease. Many common infections are more frequent and severe in the diabetic and might involve the skin, urinary tract, and other body sites such as the gallbladder and liver. Infections involving the respiratory system and the oral cavity can also commonly occur in the diabetic.

In the meantime, the diabetic condition must be meticulously managed because the immune function of the patient will be compromised so long as the patient remains uncontrollably hyperglycemic. The infection itself will cause diabetic decompensation because of the endogenous hypersecretion of stress hormones such as cortisol and the uncontrolled diabetic condition will lead to worsening of the infection. Suffice it to say that no infection should ever be considered as routine in the diabetic.

TREATMENT OF PATIENTS THAT HAVE INFECTIONS THAT CAUSE IMMUNOCOMPROMISE TO THE HOST

Canine and Feline Parvovirus Infection

Any unvaccinated dog can acquire this enteric viral infection, but puppies are much more susceptible to the devastating effects of this disease. Once the virus attacks the intestinal epithelium and destroys the mucosal defense barrier, the patient is subsequently predisposed to secondary infection to bacteremia and enterotoxemia caused by the bowel gram-negative bacterial organisms. Any accompanying neutropenia will further weaken the host's immune system. The medical treatment of these patients requires meticulous fluid and electrolyte therapy and broad-spectrum antibiotics that have particular activity against the gram negative bacteria. Other treatments have included fresh whole blood or plasma in order to correct the losses that result from the transient protein-losing-enteropathy and hyperimmune plasma. The increased amounts of IgG in the hyperimmune plasma has been purported to be of benefit to some parvovirus-infected patients. Much of what has been stated for dog can be applied to the cats that are infected with feline parvovirus.

Feline Leukemia Virus (FeLV) Infection

Feline leukemia virus belongs to the retrovirus group. It can cause a variety of clinical signs with disorders involving hematopoiesis, malignancy, myelosuppression, and infectious diseases. Diseases associated with immune suppression account for the large proportion of morbidity and mortality of FeLV-infected cats. The virus can be detected with several commercially available ELISA and immunochromatographic assays. A direct fluorescent antibody test is also available for the detection of the cell-associated p27 antigen. The disease is similar to that in human patients who are infected with the immunodeficiency virus. The affected cat can develop thymic atrophy and its lymph nodes can have depleted numbers of paracortical lymphocytes. Lymphopenia and neutropenia can occur. The FeLV-infected cat can have suppressed cellular and humoral immunity thus predisposing it just about any type of infection. Infections in these patients must be treated meticulously but the prognosis is always guarded because of the cat's impaired immune status. Giving glucocorticoids and myelosuppressive drugs is risky in these patients because of their tendency to further compromise the immune system. Cats with FeLV-associated myelosuppression have a particularly dismal outlook because of the pancytopenia that occurs and its associated consequences, namely sepsis, bleeding, and poorly responsive anemia.

Treating FeLV infected cats should emphasize its overall well-being. The environment should be stress free and the diet should be nutritious and palatable. Granulocyte colony stimulating factor (1–5 micrograms/kg SQ) and erythrocyte colony stimulating factor (100 units/kg SQ q48h and then as directed) can be used with the usual precautions to treat virus associated neutropenia and anemia. Various chemotherapeutic drug combinations are used to treat lymphoma and leukemia and these treatment protocols are readily available elsewhere. Various antiviral drugs similar to those used in humans have been attempted with vague results; these are described elsewhere. Various immune modifying drugs have been used again with vague results and these have been described elsewhere. The names of some of these drugs are interferon-alpha, parapoxvirus, acemannan, staphylococcus protein A, levamisole and others.

Feline Immunodeficiency Virus (FIV)

Feline immunodeficiency virus is a Lente virus that shares many properties of other lentiviruses such as human HIV. The clinical signs of infection are nonspecific and can include fever, dermatitis, otitis, stomatitis-gingivitis, neurological dysfunction, uveitis, conjunctivitis, chronic weight loss, enteritis, abscesses, renal dysfunction and respiratory tract infection. Although FIV had been thought to be a predisposing factor to various diseases such as cryptococcosis, toxoplasmosis, cryptosporidiosis, and bartonellosis, subsequent studies have not proven that correlation. However, the list of FIV and associated infections and various neoplasms is substantial.

The hallmark of FIV disease is a progressive dysfunction of the immune system. Loss of CD4+, CD8+, and B cells has been documented in lymph nodes, spleen, and thymus of FIV infected cats. Ultimately the loss of CD4+cells impairs both humoral and cellular immunity. FIV infection is also disruptive to cytokine production, which normally act as the mediators of the inflammatory response. The disease can be diagnosed with commercially available ELISA test that detects specific FIV antibodies.

Treatment of FIV cats broadly falls into categories of antiviral chemotherapy, immune modulatory therapy, and basic good patient care. The reader is referred elsewhere for detailed descriptions involving these treatment options. All of the currently available antiviral drugs are those developed for treating HIV in humans and these might not be readily available to veterinarians because of expense and limited supplies. The immunomodulatory drugs such as acemannan, staphylococcus protein A, and Propionibacterium acnes had been advocated for the restoration of improved immune function but there have been no well designed scientific studies to support their efficacy.

When associated diseases are diagnosed in FIV-infected cats, they should be treated with the appropriate pharmacologic drugs and supportive care because they can very well respond favorably to these treatments.

FELINE VACCINATION IN 2008: PROGRESSIVE PRACTICES FOR PROGRESSIVE PRACTICES

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GENERAL CONCEPTS

Dramatic changes have occurred in the past 10 years regarding the way veterinarians view vaccines and vaccination practices. The concepts of core and non-core vaccines, disease risk assessment, extended inter-vaccination intervals, and using products that minimize vaccine-associated inflammation are currently mainstream veterinary medicine. There are now a number of publications that document the long duration of immunity provided by most feline viral vaccines. The third revision of the American Association of Feline Practitioners (AAFP) Vaccination Guidelines for cats was published in late 2006. This very thorough document is exhaustively referenced and is an outstanding resource for veterinary practitioners as they change vaccination practices.

While a direct association between post-vaccinal chronic inflammation and risk of vaccine-associated sarcoma (VAS) has not been established, adjuvants are known to cause chronic inflammation and have been found histologically in sarcomas. The AAFP Feline Vaccine Advisory Panel suggests that, after considering all available evidence, veterinarians use less inflammatory products whenever possible. The AAFP is careful to state that the impact of adjuvants in VAS is currently unknown.

CORE VACCINES FOR CATS

Core vaccines should be given to every patient regardless of lifestyle. For cats, the core vaccines include: parvovirus (panleukopenia), herpesvirus (feline viral rhinotracheitis), calicivirus and rabies.

Modified live (MLV) FVRCP vaccines are recommended because they are not adjuvanted and do not carry the same risk of inducing chronic vaccine site inflammation as killed adjuvanted vaccines. In addition, a recent study has shown more rapid development of immunity against feline parvovirus in kittens given MLV FVRCP compared to those given killed FVRCP vaccine.

Feline leukemia virus (FeLV) vaccine is still on the AAFP non-core list, but I consider it a core vaccine for pediatric patients. I recommend that a non-adjuvanted FeLV vaccine that reduces the potential risks associated with adjuvants be used. The reason for recommending universal kitten-hood protection against FeLV is because cats under a year of age are at greatest risk for acquiring this disease. Virtually 100% of kittens infected with FeLV at 6 weeks of age or less will remain persistently infected for life. At 6 months of age, the risk of persistent infection drops to 30% and this decreases further to 5% or less after 12 months due to the development of natural resistance to this disease with age. When we ask clients about their kitten's environment, they may tell us that the kitten will be kept only indoors. However, the kitten may escape or the client may begin allowing the cat outside. The owner may not return the kitten for FeLV vaccination after the pediatric vaccination series has been completed even though the kitten's risk of exposure to FeLV has changed. By vaccinating the most susceptible individuals (young kittens), we will provide the best possible protection during the period of highest susceptibility to the disease. After a year of age, if the cat truly is kept only indoors without exposure to FeLV-infected cats, we do not need to continue FeLV vaccine administration.

What about virulent systemic calicivirus? For answers to FAQs about this disease, see the following article in this proceedings.

Chlamydophila and *Bordetella* are on the AAFP non-core list and I do not recommend giving either of these to household pet cats. Both of these diseases are very uncommon causes of upper respiratory disease and these vaccines are reactive and have a short duration of immunity. *Chlamydophila* or *Bordetella* bacterins may be helpful for short-term use in shelter or cattery situations where an outbreak of upper respiratory disease has occurred if these agents are cultured from a number of cats and confirmed as a major component of the respiratory syndrome.

The feline infectious peritonitis (FIP) coronavirus vaccine and feline *Giardia* vaccines are on the AAFP not recommended list.

I do not recommend the currently available feline immunodeficiency virus (FIV) vaccine because the vaccine is adjuvanted and will result in false-positive results when cats are tested for FIV. FIV-vaccinated cats will test falsely positive on antibody-based tests (ELISA, Western Blot, IFA) for at least a year post vaccination. FIV PCR testing is not yet sufficiently accurate to help us differentiate vaccinated from naturally infected cats.

PEDIATRIC VACCINATION

The goal of pediatric vaccination is to stimulate active and solid immunity before the susceptible kitten is exposed to pathogenic organisms. This means that we must start a vaccination program early enough to prevent active disease as maternal antibody wanes.

The pediatric core FVRCP vaccine series should be started when the kitten is seen for its first pediatric examination at 6 to 8 weeks of age. Core vaccines should be repeated at 3- to 4-week intervals until the kitten is 16 weeks of age. Although some biologics manufacturers have experimental studies that demonstrate good protection by 12 weeks of age, recent research using conventional kittens indicates that maternal antibody interference with vaccination may persist in some kittens beyond 14 weeks of age. Therefore, I recommend administering the final pediatric vaccination at 16 weeks of age or older. Rabies vaccine should be given at 12 weeks of age or older as per the Rabies Compendium and state/local ordinances. I recommend using a non-adjuvanted rabies vaccine.

Kittens should be tested negative for FeLV prior to vaccination. In addition to the other serious consequences of infection, there is no demonstrated benefit of giving an FeLV vaccine to an FeLV-infected cat. I recommend using a non-adjuvanted FeLV vaccine according to the manufacturer's instructions.

What if a client is late for revaccination during the pediatric series or comes back at 6 months of age for neuter without having completed the pediatric series? Must I start the vaccination series all over again?

No. If the last core FVRCP vaccine was given at 12 weeks of age or older, one more MLV vaccine should suffice to ensure solid protection. If the last vaccine was at less than 12 weeks, a series of two MLV vaccines is recommended.

Similarly, if you are evaluating an older cat of unknown vaccination status, a series of two MLV FVRCP vaccines, in addition to one rabies vaccination (RV) is recommended to assure a solid basis of protection. After that, for adults, the revaccination interval for FVRCP is 3 years, RV at one year and then as per manufacturer's instructions or state/local ordinance thereafter.

RE-VACCINATION INTERVALS

FVRCP, FeLV, and RV should be repeated at one year of age. FVRCP is given every 3 years after that time. RV should be re-administered according to the manufacturer's licensing approval (1 year or 3 years) and according to state/local ordinance. FeLV vaccination may be continued according to manufacturer's instructions if the cat is at risk of exposure after 1 year of age.

Is it better to use an adjuvanted 3-year licensed RV or a non-adjuvanted 1-year licensed RV in cats? An important factor in induction of VAS is chronic inflammation at the injection site. Experimental histologic studies of vaccination sites show that non-adjuvanted vaccines produce little to no inflammation, whereas adjuvanted vaccines cause inflammatory changes at the site that may persist. In my opinion, it is better to use a non-adjuvanted vaccine more frequently rather than any adjuvanted vaccine, regardless of the frequency of use.

What if I change the vaccine products I am using? Must I start the vaccine series all over again? No. The body does not recognize vaccine brand names. The important protective antigens will be present in a product produced by a different manufacturer. All approved veterinary vaccines have been tested and licensed as effective by the USDA.

VACCINE ADVERSE EVENTS

Systemic Adverse Events

It is fairly common for cats to exhibit some malaise, low grade fever, and anorexia for 12 to 36 hours post vaccination. We see this adverse event so commonly that most veterinarians warn cat owners that this will occur.

"Limping kitten syndrome" is a post-vaccinal, febrile, nonerosive polyarthritis syndrome associated with calicivirus vaccine administration. As the name suggests, this syndrome is most common in young cats. The polyarthritis is a self-limited and usually lasts less than a week. Nonsteroidal anti-inflammatory drugs (NSAIDs) or other analgesic treatment will provide relief and shorten the duration of clinical signs.

Immune-mediated hematologic disorders including immune-mediated anemia, thrombocytopenia, and/or pancytopenia have occasionally been associated with vaccine administration in cats. Post-vaccinal anterior uveitis has been reported in a few cats. This appears to be an Arthus-like immunologic reaction similar to the "blue-eye" reactions seen with canine CAV-1 vaccine. These immune-mediated disorders usually appear within 3 to 4 weeks post-vaccination.

The most critical, life-threatening adverse vaccine reaction is systemic anaphylaxis. Cats may exhibit a shock-like event with collapse, panting, vomiting, and/or diarrhea. Intravenous fluids, rapid-acting corticosteroids and antihistamines should be administered as soon as possible. The lung is a major shock organ in cats and an enriched oxygen environment may be helpful. Avoid over-aggressive fluid administration because pulmonary edema can result.

Cats with a history of adverse vaccine events should be carefully assessed for the need for any vaccines in the future. In general, we try to avoid revaccination whenever possible. If additional vaccines must be given, they should be given individually and separated by a 3- to 4-week interval. A different brand/type of vaccine should be used and the cat should receive antihistamine and corticosteroid pre-medication. I recommend that pre-treatment and vaccination be given as early in the day as possible, and the cat should remain at the veterinary hospital for observation for the remainder of the day.

Vaccine-Associated Sarcoma (VAS)

The issue that galvanized the veterinary community and stimulated us to reassess vaccination practices, particularly in cats, has been the emergence of vaccine-associated sarcomas. This often fatal consequence of vaccination did not appear in cats in significant numbers until killed, adjuvanted rabies and feline leukemia virus vaccines were introduced. Vaccine adjuvants can induce chronic inflammation at injection sites that may be associated with sarcoma development in genetically predisposed cats. Aluminum is not the only component that is associated with VAS, however, aluminum serves as the "smoking gun" in injection-site tumors because it has been identified in macrophages in sarcomas and no other commonly used injectable agents contain this material. The histologic appearance of VAS is classical because they have a significant lymphocytic and plasmacytic infiltrate. The etiology can be further confirmed with immunohistochemical studies.

There is probably a genetic component that predisposes some cats to tumor development at sites of chronic inflammation. At present we are not able to test for this genetic predisposition. Mechanical influences such as the temperature of the vaccine, the size of the needle used for injection, and the site of injection (subcutaneous versus intramuscular) have been ruled out as causal factors.

There are several significant problems with using retrospective epidemiologic studies to attempt to determine which specific products or adjuvant components are of most concern. First, veterinarians often change products and may not keep accurate records about which product brands and lot numbers were used. Second, tumors may develop many years after a vaccine was given. Therefore, if a VAS tumor develops in a 10-year-old cat that has been vaccinated yearly, we cannot know whether it was the vaccine given this year, 5 years ago, or 9 years ago that produced neoplastic transformation.

The occurrence of VAS in cats has been listed in various reports to be between 1.3:1000 and 1:10,000. Cats tend to breed locally, not nationally or internationally. Local populations may have genetic variations that may predispose a cat to developing VAS. Thus, the incidence of VAS seen in a particular practice may be different from another practice 10 or 100 miles away that uses the same vaccines and protocols.

How do you I know whether my patient has a VAS and what should I do if I diagnose one? A local reaction at the site of vaccination is relatively common in cats, especially when adjuvanted vaccines are used. This site reaction usually subsides within 3 to 4 weeks without incident. If the site lesion is still present 4 weeks post vaccination, you should perform fine needle aspiration cytology. If only inflammation is seen, the site can be watched for an additional 4 weeks. If the local reaction is still present 8 weeks post vaccination, it should be biopsied and if not neoplastic, the affected area should be excised. If there is neoplastic transformation at a vaccination site, the cat should be referred for imaging and radical surgical removal of the mass. Complete first excision is the best treatment and may be curative. Further adjunctive therapy for VAS might include radiotherapy (brachytherapy, etc.), chemotherapy, and/or immunotherapy. The specifics of these adjunctive treatments are beyond the scope of this discussion.

Using the AAFP recommended sites for vaccination gives us a better chance to remove vaccination-site sarcomas completely should they occur. However, it is best to give non-inflammatory feline vaccines on an appropriate, reduced frequency schedule as recommended by the AAFP, ACVIM Infectious Disease study group, AAHA, and academic infectious disease specialists.

Lymphocytic Nephritis from Parenteral Feline Vaccines Grown in Crandall Rees Kidney Cells

Chronic progressive renal disease (CPRD) is the most common cause of morbidity and mortality in older cats. Lymphocytic/plasmacytic nephritis is a common histologic finding in cats with CPRD. A pilot study by Dr. Mike Lappin and his research group several years ago demonstrated that Crandall Rees kidney cell (CRFK) antigen from viral cell cultures used to produce feline vaccines caused the development of anti-renal antibody in cats vaccinated with parenteral FVRCP vaccines. A further report from this research group demonstrated lymphocytic/plasmacytic inflammation in the kidneys of CRFK-sensitized cats. While the long-term significance of these findings is not yet known, it is another reason to modify our vaccination protocols to reduce the number of vaccines and vaccinations given to a cat to the fewest needed to maintain good disease protection and good health.

REPORTING ADVERSE EVENTS

Veterinarians should keep accurate records of the brand, lot, serial number and injection site of all vaccines administered to their patients. The peel-off vaccine labels are very useful for those practices using paper records. Data should be entered in the electronic record for paperless practices. Any suspected adverse event should be reported to the Professional Services veterinarians of the biologics manufacturer involved. Adverse events should also be reported to the USDA Adverse Event reporting site at: http://www.aphis.usda.gov/vs/cvb/html/adverseeventreport.html. If entering this long string is cumbersome, you can "Google" USDA adverse event, and the reporting site will be the first entry on the search results list. The USDA online reporting form is very easy to fill out and submit.

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NATIONAL INCIDENCE OF METHICILLIN-RESISTANT STAPHYLOCOCCUS INFECTIONS: UNDERSTANDING, TREATMENT AND PREVENTION

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METHICILLIN-RESISTANT *STAPHYLOCOCCUS AUREUS*

Methicillin-resistant *Staphylococcus aureus* (**MRSA**) is a major noscomial pathogen in human hospitals and extended care facilities and of late as a serious infectious pathogen in the community population not exposed to these institutions. Important contributors to the increasing importance of this pathogen include:

- **Pattern of resistance** to a wide range of antibiotics besides beta-lactams (penicillins and cephalosporins). Hospital-acquired MRSA (HA-MRSA) had been differentiated from the community-acquired MRSA (CA-MRSA) by its more extensive resistance. However, lately CA-MRSA is showing multiple resistance profiles blurring the line between these two categories.
- **Opportunistic nature of the pathogen.** *S. aureus* is a commensal organism in people. The nasopharanyx is the major source of the organism, although it can also be carried in other sites, including the intestinal tract. Studies have show that up to 30% of people have *S. aureus* in their nose at any point in time. Hands are a major source of transmission.

  MRSA strains are usually not considered more intrinsically pathogenic than other coagulase-positive *Staphylococcus* spp. However, some strains of CA-MRSA do appear to be more infectious and readily transmissible.

  Major morbidity and mortality as associated with HA-MRSA colonizes a susceptible host (hospitalized patient, immunocompromised or debilitated individuals) and subsequently causes an opportunistic infection that fails to respond to conventional treatment. However, CA-MRSA is now being seen as a cause of extensive skin infections in otherwise healthy individuals gaining access through fomites (blankets and towels) and small skin abrasions leading to supprative spreading lesions.
- **Mechanism of resistance.** There are two mechanisms of resistance in methicillin-resistant *Staphylococcus* (MRS) organisms:
  - **Penicillin-binding proteins.** All penicillins and cephalosporins (beta-lactams) require binding to a penicillin-binding protein (PBP) located in the bacterial cell wall to initiate their activity. MRSA produces a defective low-affinity PBP (PBP2a) due to the presence and activation of the **mecA gene.** The mecA gene itself comes from a novel integrative and mobile genetic element called a Staphylococcal Cassette Chromosome (**SCCmec**) that conveniently is bundled with its own enzymes need to excise it from the cassette and insert itself into the Staph's chromosomal structure. This method of acquisition is unique to this mechanism and the spread of MRSA is usually through clonal expansion rather than the normal process of mutation or plasmid-mediated transfer. All MRSA can be traced back to a single clone found in Europe in the mid 1960s.
  - The binding affinity of penicillins and cephalosporins to PBP2a is very low, disabling its ability to disrupt cell wall synthesis and rendering the drug ineffective. The presence of PBP2a on a *Staphylococcus* organism confers resistance to ALL penicillins and cephalosporins.
  - **Cell-wall thickening**: MRSA also has a thick cell wall that makes penetration by antibiotics difficult, conferring resistance to multiple antibiotics (not just beta-lactams).
  - **Efflux Pump**: Acquired through other means then a mecA gene, these proteins are involved in active removal of antibiotics through a membrane-bound pump, limiting many families of antibiotics that work on internal structures.

METHICILLIN RESISTANCE OF STAPHYLOCOCCAL INFECTIONS IN VETERINARY MEDICINE

MRSA has been reported in animals (mostly in Europe) but was considered uncommon in domestic pets and rarely caused disease. *S. aureus* is not a commensal organism of dogs or cats and is considered a transient pathogen acquired from its primary host, humans. Since 2005, there has been a rapidly growing body of work as well as data that shows an alarming acceleration of MRSA cultures from both dogs and cats from almost all body sites routinely tested. When present, MRSAs that have been strain typed have been shown to be exactly the same organism that colonizes people. The studies to date indicate MRSA infections are human-to-pet transmission and are not considered a part of the normal colonizing flora and thus only transiently colonize domestic pets.

Culture Incidence

MRSA is most frequently cultured from canine wounds, abscesses, and chronic pyodermas. In these cultured sites *S. aureus* (SA) accounted for 3% to 5% of all bacteria cultured, which has remained unchanged since 2005. What has changed is the proportion of those SA which are MRSA. In 2005, only 19% were MRSA while in 2007 the percentage has significantly increased up to 42%. This is an unusual phenomenon in veterinary medicine, where infectious disease experts always implicate antibiotic use as contributing to increasing resistant human pathogen. In this case, SA comes from humans and in 2007, almost half of the SA infections transmitted were MRSA. The rise in resistant organisms in humans is now affecting their pets.

In these same cultures, *Staphylococcus intermedius* (SI), the commensal Staphylococcus of dogs and cats, is identified in 25% to 30% of all wound cultures. In 2004, no MRSI organisms were cultured. In 2005 3.1% of all MRSI cultured from wounds were methicillin resistant and in 2007 the number has increased significantly to 10.2 % ($P < 0.05$). These pathogens are not transmitted from humans, where they play very little if any process in infections; they were created most likely via horizontal transfer of the MecA gene. The mechanism for this transfer is unclear; however, it has been reported that the mecA gene is present in *S. intermedius* isolates with one study demonstrating it in almost 50% of isolates tested. The data is clear that while the rate of wounds infected with Staphylococcus has remained the same over the past 3 years, the percentage of those staphylococci, either from humans or pets has vastly increased.

TESTING FOR METHICILLIN RESISTANCE

- Methicillin resistance can be tested using any of the beta-lactamase stable penicillin drugs (including methicillin), although oxacillin is most commonly used. The borders of the zone of inhibition can be more difficult to read with oxacillin, due to a delayed onset of resistance observed during testing. The mecA gene is inducible, so in clinical practice a patient may appear to have a sensitive Staph when in fact the antibiotic induces its own resistance. In the lab this means MRSAs appear sensitive to oxacillin at 24 hours but not at 48 hours.
- Cefoxitin is a much better inducer of the mecA gene, so potential resistance (if present) is seen in the first 24 hours more reliably, and is currently the recommended test.
- Latex agglutination test for the pbp2a protein. This is becoming a more routine test in human medicine as the quickest test for MRSA detection. However preliminary work on veterinary pathogens has shown it to be less reliable as an indicator of methicillin resistance. The vast majority of *S. intermedius* isolates in dogs and cats do not show methicillin resistance.
- However, literature reports on *S. intermedius* isolates from dogs and cats and methicillin resistance have given conflicting results: From University of Tennessee, with 57 *S. intermedius* isolates, only 2 were methicillin resistant, although 50% had the mecA gene detected by PCR testing, suggesting that it may not have been expressed. From the University of Illinois, of 25 methicillin-resistant *S. intermedius* isolates, 23 had the mecA gene, and the non-methicillin-resistant isolates did not have the mecA gene. Further work is needed to determine the value of mecA gene detection on veterinary isolates.

METHICILLIN-RESISTANT STAPHYLOCOCCUS (MRS)

Of more concern in veterinary medicine is the potential for host adapted staphylococcal species to acquire the resistance patterns seen in MRSA. *S. intermedius* is the coagulase-positive commensal *Staphylococcus* spp. of dogs and cats. Coagulase negative *Staphylococci* (such as *S. schleiferi* subsp *schleiferi*) isolates in dogs and cats appear to be more commonly detected with methicillin-resistance than the coagulase positive isolates. These are usually reported from canine pyodermas. *S.schleiferi* subsp *coagulans* is more commonly identified from ear cultures. Antech Diagnostics has just started reporting on this organism in December 2007.

TREATMENT OPTIONS FOR MRS

Lack of clinical response to any beta-lactam (penicillins or cephalosporins) , even if in vitro testing indicates that they are sensitive, indicate that these antibiotics should NOT be used to treat an MRS infection. Other choices include:

- Chloramphenicol
    - Chloramphenicol remains the ONLY excellent drug of choice in MRS infections with a predictable in vitro efficacy >95% from over 1,000 cultures of MSA.
    - Dosing of 33 mg/kg TID in dogs
    - Dosing of 50 mg/cat BID
- Potentiated Sulfonamides
    - Better than average success against MRS at 55% sensitivity but clinical studies in man are conflicting as to its use even from cultured MRSA deemed sensitive in vitro.
- Clindamycin
    - Although found effective in many human CA-MRSAs, the experience at Antech Diagnostics has show the antimicrobial to be effective in less than 50% of the MRS isolates.
- Quinolones
    - Enrofloxacin, marbofloxacin, and difloxacin all show less than a 50% in vitro efficacy indicating a multiple resistance mechanism in the MRSA and MRSI that are being cultured.
- Vancomycin
    - Vancomycin is a drug that is sensitive to the vast majority of all MRS organisms.
    - Several disadvantages: It is very nephrotoxic in dogs, and must be administered q 6 h by IV route with concomitant IV fluids.
- Zyvox (Linezolid)

One of a new family of antibiotics (oxazolidinones); can be administered orally or parenterally. Pharmacokinetic evaluation in dogs indicates the effective dose is 20–30 mg/kg q 12 h. These antibiotics have low toxicity, but are very expensive. Use only if no other choice is effective; for example, in multi-drug resistant MRS. Zyvox is also effective against even vancomycin-resistant enterococcus.

CANINE VECTOR-BORNE DISEASES WITH AN EMPHASIS ON NORTH AMERICA

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In North America, fleas, mosquitoes, and ticks are considered the most important vectors for a spectrum of infectious agents that can induce disease in dogs. In regard to canine vector-borne diseases, the vector competence of fleas for the transmission of several potential vector-borne pathogens has not been extensively studied. Fleas are known to carry and potentially transmit *Bartonella henselae, Bartonella clarridgeae, Bartonella quintana, Mycoplasma hemofelis, Rickettsia felis, Wolbachia* species, and *Dipylidium caninum*. Fleas act as an intermediate host for the tapeworm *D. caninum,* and can be a source of infection for cats, dogs and human beings, following ingestion of the flea. *Bartonella henselae* is also a zoonotic organism that can be transmitted to cats (and perhaps to dogs) by ingestion of flea feces containing viable *B. henselae* organisms. Surprisingly, *B. henselae* can remain viable in flea feces for periods up to at least 15 days. *Bartonella henselae* causes cat scratch disease, endocarditis, regional or generalized granulomatous lymphadenitis and numerous other disease manifestations in people. Although cat bite or scratch transmission of *B. henselae* to dogs has not been proven, we have isolated the organism from young dogs with polyarthritis and a history of cat scratches. If true, this would suggest that flea infested cats are a risk factor for transmission of this organism to dogs. In dogs, both *B. henselae* and *B. clarridgeae* have been shown to cause endocarditis; therefore, both of these flea-transmitted organisms can be pathogenic in dogs.[3] Recently, our research group has documented chronic intravascular infection in people (veterinarians, veterinary technicians and wild life biologists) with extensive arthropod exposure and animal contact.[5] Ultimately, it may be proven that a flea infestation in dogs, as has been shown for cats, leads to a persistent relapsing *B. henselae* bacteremia, with transmission to people via bite (salivary inoculums) or scratch (flea feces inoculums). In recent years, there has been a rapid expansion of clinically relevant information relative to canine and feline hemoplasma infections. Hemotropic mycoplasmas (previously known as *Haemobartonella* or *Eperythorozoon* species) can cause a hemolytic anemia in cats, dogs and other animal species. As *Mycoplasma* species are cell-wall deficient bacteria, these organisms are difficult or impossible to culture from patient samples. With the advent of polymerase chain reaction (PCR) assays that allow for the diagnostic targeting of organism-specific gene sequences in patient samples, infection with hemotropic *Mycoplasma* species is now known to be a prevalent finding in healthy cats and dogs, as well as those with anemia. Similar to *B. henselae*, these bacteria can most likely be transmitted by fleas, induce chronic intravascular infections and potentially participate as the primary or cofactor in disease expression (including anemia). Unique *Mycoplasma* spp., including *M. hemocanis* and 'Candidatus *Mycoplasma hemoatoparvum*,' infect dogs and occasionally a feline-adapted *Mycoplasma* species can be found in the blood of a dog. As with other vector-borne organisms, hemotropic *Mycoplasma* species have evolved to induce persistent intravascular infection, without inducing disease. Therefore, co-infection, sequential infection or concurrent development of a noninfectious disease is necessary for a given *Mycoplasma* species to induce a hemolytic crisis. Also similar to *B. henselae,* there is increasing experimental evidence to support direct salivary transmission of *Mycoplasma* species among cats. Similar to FeLV, aggressive interactions among male cats may be an important means of transmission. Transmission via saliva or vectors is poorly characterized in dogs. As has long been established mosquitoes transmit *Dirofilaria immitis*, the cause of heartworm disease, to dogs. Recently, a *Wolbachia* endosymbiont has been identified within both adult and microfilaria of *D. immitis*. Evolving evidence suggests that these organisms may play a role in the pathogenesis of the vascular injury, which has been historically attributed solely to the adult worms or microfilariae. Recent studies have shown that both dirofilarial and *Wolbachia* antigens, induce interactions within the host that result in the development of the pathology and in the regulation of the host's immune response during canine, feline and human heartworm infections. The above observations and others support comprehensive evaluation of the type, frequency and extent of vector exposure. Obtaining a comprehensive vector exposure history is an important component of the annual examination process for healthy or sick dogs. The expanding number of known tick-borne organisms, the broad geographic distribution of many tick species, the ability of tick-borne organisms to induce chronic intravascular infections, and the highly pathogenic potential of some tick-borne organisms makes tick-borne infections the most important subset of canine vector-borne infectious diseases in North America. The remainder of this article will highlight new information related to various tick-borne pathogens.

During the past decade, tick-transmitted infectious diseases have become increasingly important in the United States and throughout much of the world. Several factors, including the ongoing Lyme disease epidemic, suburbanization of tick habitat, the rapid increase in deer numbers as well as other wildlife populations that reside within the peri-domestic environment, the recognition that same species and strains of tick-borne pathogens can induce disease in pets and their owners, and the widespread availability of safe and effective acaricides have all contributed to enhance the awareness of tick-borne infections among both professionals and non-professionals. In conjunction with the above factors, there has also been a concurrent discovery of new tick-borne organisms, for which clinical, epidemiologic and pathologic data is minimal or lacking, particularly in regard to disease causation in animals. Examples include *Borrelia lonestari, Borrelia turicatae, Rickettsia felis*, and *Rickettsia amblyommi.*

For nearly two decades, our research group has contributed to the development of diagnostic, therapeutic and preventive strategies for the management of infections caused by tick-transmitted intracellular organisms. As a result of these research efforts, and those of many other investigators throughout the world, we continue to gain an increasingly unique perspective on the clinical and immunopathologic consequences of tick-borne infectious diseases. It has been stated that: "Ticks are only interested in nutrition (a blood meal) and sex (ie, perpetuation of the species)." Although the tick might object to this simplistic view of its complex lifestyle, bacteria, protozoa and viruses have used the predictable behavior of all tick species to facilitate their transmission and therefore the perpetuation of their species. Transmission of a tick-borne organism is most frequently accomplished when the tick obtains a blood meal; however, transmission can occur when the tick is inadvertently ingested by a dog (*Hepatozoon canis* or *Hepatozoon americanum*). In those instances, when tick-transmission is the sole means by which an organism such as *Ehrlichia canis* is transmitted from one infected dog to a previously noninfected dog, and when the dog is the only known reservoir host for *E.canis*, it becomes obvious that *E. canis* would evolve to be efficiently transmitted by a tick (*R. sanguineus*) for which all three tick life cycle stages (larvae, nymph and adult) preferentially involve feeding on dogs. It is equally obvious that *E.canis* would seek to induce long-lasting infection, accompanied by minimal pathogenicity to the dog (do not destroy the home you live in) and the organism would infect a cell (the monocyte) that would facilitate transfer of *E. canis* to additional blood seeking ticks. This evolutionary arrangement benefits *E. canis*, but does not appear to benefit the dog, which can develop disease manifestations ranging from epistaxis to pancytopenia. Although it is difficult to determine the factor(s) that induce disease causation when a dog is infected with a highly adapted vector-borne organism such as *E. canis*, it is certain that sequential or simultaneous infection with another vector-borne organism can contribute to more severe hematological or immunologic aberrations and a more severe course of illness. Unpublished data from our laboratory indicates that many dogs appear to immunologically eliminate *E. canis* following tick-transmission, as opposed to developing chronic infection. Tick-borne organisms such as *Anaplasma phagocytophilum* and *R. rickettsii* typically induce acute, severe illness, whereas other organisms such as *Babesia canis, Babesia gibsoni Bartonella vinsonii* subsp. *berkhoffii* and *E. canis* can induce chronic, insidious illness. As described briefly above, specific tick species preferentially transmit different pathogenic organisms, dogs can be sequentially or simultaneously infested with more than one tick species, and a single tick can transmit more than one organism leading to co-infection. Both the tick species and the organisms that they transmit can vary substantially within and between various geographic regions. For example, infection with *R. rickettsii*, transmitted by *Dermacentor variablis* in the state of North Carolina, occurs much more frequently in the piedmont region (central part of the state) as compared with the eastern costal plain or the western Appalachian mountain range. All of the above factors make the diagnosis and medical management of tick-borne infectious diseases a complex and challenging task for the practicing veterinarian. Without question, the old adage "An ounce of prevention is worth a pound of cure" is applicable to any discussion of tick-borne infectious diseases. The advent of new, safe and long-lasting acaracides that can repel and kill ticks makes the prevention of tick-borne diseases an important priority for veterinarians and pet owners throughout the world. Based upon experimental infection studies, using tick attachment models, application of acaracide products can decrease the risk of transmission of *Borrelia burgdorferi*, the cause of canine Lyme borreliosis. There is the need for additional studies to define the extent to which commercially available acaracides can prevent infection with various tick-borne organisms in North America.

SPOTTED FEVER GROUP RICKETTSIAE AND ROCKY MOUNTAIN SPOTTED FEVER

Spotted fever group (SFG) rickettsiae have been described from all continents. In North America, *Rickettsia rickettsii* is the most important SFG rickettsiae because this tick-transmitted organism can cause serious or fatal illness in dogs and people. The SFG group includes numerous closely related species including *R. rickettsii* (the type species), *R. africae*, *R. akari, R. australis, R. conorii, R. felis, R. montana, R. parkeri, R. rhipicephali* and *R. sibirica*, although many other SFG rickettsiae have been described. The typhus group rickettsiae, which includes *Rickettsia typhi* and *Rickettsia prowazekii,* has not been implicated as a cause of illness in dogs and experimental infection of dogs with typhus group rickettsiae in our laboratory did not result in disease. Throughout various regions of the world, spotted fever group rickettsiae are transmitted by *Amblyomma, Dermacentor, Haemaphysalis, Ixodes* and *Rhipicephalus* tick species. Regardless of the strain or species of SFG rickettsiae, these organisms generally induce an acute febrile illness secondary to endothelial cell damage, which results in vasculitis, altered vascular permeability, edema and necrosis. To date, chronic infection with a SFG rickettsiae has not been confirmed in dogs or human beings. Although it seems likely that other SFG rickettsiae could induce disease in dogs, only *R. rickettsii* in North America and *R. conorii* in southern Europe have been documented as canine pathogens. Historically in North America, only *Dermacentor variabilis* (south and eastern United States), and *Dermacentor andersonii* (north western US and Canada) were known to transmit *R. rickettsii* to dogs or human beings. There is now strong epidemiological evidence that a recent outbreak of RMSF in a nonendemic area of Arizona was caused by *Rhiphicephalus sanguineus* (the brown dog tick). This tick species prefers to spend all three life cycle stages (larvae, nymph and adult) on a dog. When the environment is infested with large numbers of brown dog ticks or if dogs are removed from tick infested house, human blood becomes an acceptable, if not an attractive alternative. In this setting, both *R. rickettsii* and *Ehrlichia canis* can be transmitted to human beings. In the context of morbidity, mortality and severity of disease, RMSF is the most important tick-borne infection of dogs in the United States. Due to variation in the severity and location of vascular lesions among different patients, veterinarians should anticipate a spectrum of disease manifestations following naturally occurring infection with *R. rickettsii.* Much of the United States is considered endemic for the ticks (*Dermacentor variabilis, Dermacentor andersoni, Rhipicephalus sanguineus*) that transmit *R. rickettsii. Rickettsia rickettsii* infection ("Rocky Mountain spotted fever") also occurs in areas of Central and South America, where several outbreaks of fatal human illness has been reported. Clinical abnormalities associated with RMSF include fever, anorexia, depression, mucopurulent ocular discharge, scleral injection, tachypnea, coughing, vomiting, diarrhea, muscle pain, neutrophilic polyarthritis, and a diverse group of neurologic signs including hyperesthesia, ataxia, vestibular signs, stupor, seizures, and coma. In some dogs weight loss is very severe, considering the short duration of illness. Poorly localizing joint, muscle and/or neurologic pain suggestive of polyarthritis, polymyositis, or meningitis may represent the only or most prominent clinical finding. Retinal hemorrhages are a consistent finding, but may be absent early in the course of the disease. Epistaxis, melena, hematuria, and petechial to ecchymotic hemorrhages occur in some dogs, but may not develop unless diagnosis and treatment are delayed for five or more days after the onset of clinical signs. Scrotal edema, hyperemia, hemorrhage, and epididymal pain are frequently observed in male dogs. Signs associated with cardiovascular collapse, oliguric renal failure or brain death can develop in the terminal stages of the disease. Gangrene affecting the distal extremities, scrotum, mammary glands, nose or lips is associated with severe vascular obstruction and can induce substantial tissue loss, necessitating reconstructive surgery. Clinical manifestations in dogs are identical in most instances to manifestations reported in human patients. From a public health perspective, the dog is an environmental sentinel for RMSF and therefore it is important that veterinarians recognize and accurately diagnose RMSF. Diagnostic confirmation of RMSF in a dog allows the veterinarian to discuss the risk of *R. rickettsii* transmission in the peri-domestic surroundings.

CANINE AND HUMAN EHRLICHIOSIS

At least three *Ehrlichia* spp.—*E. canis, E. chaffeensis,* and *E. ewingii*—are capable of infecting dogs and people in North America. For various reasons dogs play a seemingly minor role in the acquisition of human infections, perhaps with the exception of human *E. canis* infections in South America (and other regions of the world in which large peri-domestic *Rhipicephalus sanguineous* populations are found). Studies performed decades ago indicated that nonhuman primates could be infected with *E. canis* and more recently, an organism genetically related (or identical) to *E. canis* was isolated from a veterinarian and subsequently detected by PCR testing in other people from Venezuela. In the United States, both *E. chaffeensis* and *E. ewingii* can cause serious disease manifestations in people, including meningoencephalitis, acute renal failure and acute respiratory failure. In addition to *E. canis,* both *E. chaffeensis* and *E. ewingii* can induce ehrlichiosis in dogs.

Investigators from South Africa have obtained molecular evidence (16S rDNA sequencing) that supports infection of dogs and people with an organism that is identical or closely related to *E. ruminantium* (previously *Cowdria ruminantium*). The implications of this recent finding could prove to be of great importance, if *E. ruminantium*, the organism that causes Heartwater in cattle in Africa, were introduced into the United States by way of dog transport. Recently, a genetically similar organism (ie, an *E. ruminatium* strain) has been found in deer from the southeastern US, and in a human from Georgia, diagnosed with ehrlichiosis. *Ambylomma americanum* ticks from a park in the metropolitan area of Atlanta, GA, were used to experimentally infect a goat, which developed an acute febrile illness and remained infected (and competent to infected naïve ticks) for at least 5 months. Although not yet confirmed, infection of goats, deer and a human being suggests that this organism is most likely pathogenic for dogs.

In recent years, there have been considerable advances in defining the efficacy of various antibiotics for treatment of canine ehrlichiosis. It is now clear that 2 weeks of doxycycline is not an effective treatment for *E. canis* infection, whereas 4 weeks of therapy (doxycycline 5mg/kg every 12 hours) eliminates *E. canis* in both naturally and experimentally infected dogs. The short term prognosis following treatment for canine ehrlichiosis is generally very good. Dramatic clinical improvement usually occurs within 24 to 48 hours after initiation of doxycycline or tetracycline in dogs with acute phase or mild chronic-phase disease. Rapid clinical improvement is frequently noted in chronically infected dogs; however, periods up to a year may be necessary for complete hematological recovery. The long-term prognosis following treatment is much more variable, potentially related to failure to diagnose concurrent infections. Undiagnosed infection with a *Babesia* or *Bartonella* spp. can be misinterpreted as an ineffective therapeutic response when treating ehrlichiosis, as doxycycline is generally an ineffective treatment for babesiosis and bartonellosis. Experimentally, enrofloxacin will suppress the clinical manifestations of *E. canis* infection and may result in hematological improvement, but does not eliminate the infection. Although imidocarb dipropionate has gained clinical acceptance in some endemic regions for treating severe, chronic, or presumed refractory cases of ehrlichiosis, lack of efficacy has been demonstrated in treating both naturally and experimentally infected dogs.

MOLECULAR DIAGNOSTIC TESTING AND VECTOR-BORNE DISEASES

Molecular diagnostic approaches have begun to facilitate a "modern day" revolution in our understanding of the interactions of single or multiple infectious agents in our patients. In addition, PCR has enhanced the detection of polymicrobial infections which emphasizes the complexity of disease expression induced by acute or chronic infection, and has resulted in the redefinition of "previously understood" vector-borne diseases such as babesiosis and leishmaniasis. PCR amplification of organism-specific DNA sequences can be accomplished in a matter of hours and in most instances the detection of a PCR amplicon confirms active infection with a specific organism. This approach has distinct advantages over culture, which can require incubation times ranging from days, to weeks, to months depending on the organism. In most instances, approaches that provide rapid culture results select for only a few more easily grown organisms. Although serology or examination of the cell mediated immune response will remain an important component of infectious disease diagnosis, these tests identify evidence of immune recognition of a pathogen, but do not confirm active infection. Cross-reactivity among various infectious agents, failure to confirm active infection, and for an increasing number of infections (babesiosis, bartonellosis, leishmaniasis and others) the serological response to the organism may be minimal or non-existent, despite documentation of chronic, active infection by PCR are limitations to the interpretation of serological test results in a given patient.

Because most vector-borne pathogens are difficult, if not impossible to culture from patient samples and because many animals achieve immunologic clearance of the organism following transmission of the organism, the use of PCR to document active infection prior to or at the time of initiation of therapy or as an aid to document therapeutic elimination of the infection is gaining acceptance among veterinary clinicians. PCR testing for *Anaplasma, Babesia, Cytauxzoon* (cats) *Ehrlichia, Leishmania* and *Rickettsia* species is available through the:

Vector-borne Diseases Diagnostic Laboratory
NCSU-CVM Rm 462A
4700 Hillsborough Street
Raleigh NC 27606
Phone: 919-513-8279
www.cvm.ncsu.edu/docs/ticklab.html

SIMULTANEOUS INFECTION WITH MULTIPLE VECTOR-TRANSMITTED PATHOGENS

Recently, simultaneous infection with more than one tick-borne pathogen has been recognized with increasing frequency in human and canine patients. Obviously, simultaneous infection with more than one tick-transmitted pathogen has important diagnostic, therapeutic and prognostic implications for the individual patient. The pathophysiologic consequences of co-infection in dogs with various combinations of bacteria, rickettsia and protozoa have not been characterized clinically or experimentally. Although retrospective seroepidemiologic studies suggest that dogs may experience simultaneous infection with multiple tick-borne pathogens, microbiologic (culture) or molecular (PCR) evidence of simultaneous infection in dogs is currently limited. In nature, the risk of exposure to ticks, fleas, mosquitoes and biting flies is far greater for dogs than for human beings. In addition, dogs can be infested with hundreds of ticks, and at times infestation may involve different tick species. Therefore, the unknown influences of concurrent infection with multiple tick-borne pathogens, including *Anaplasma, Ehrlichia, Rickettsia, Babesia* and *Bartonella* species, on factors such as pathophysiology, diagnosis, prognosis or therapeutic outcome could be more readily characterized in dogs. Of 27 dogs that were investigated in a kennel due to increased mortality, 25 were seroreactive to an *Ehrlichia* sp., 20 to a *Bartonella* sp., 17 to a *Babesia* sp. and 22 seroconverted to *R. rickettsii* antigen. Based upon PCR analysis, several dogs were co-infected with multiple *Ehrlichia* species, as well as a *Bartonella, Babesia* or *Rickettsia* species. Prospective evaluation of sick dogs, managed in our teaching hospital, has yielded molecular evidence of co-infection with multiple tick-transmitted pathogens. Our recent experience indicates that dogs with heavy tick exposure can be infected at a high rate with multiple, potentially zoonotic, tick-borne pathogens.

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EMERGING VECTOR-BORNE INFECTIOUS DISEASES

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DEFINING AN EMERGING VECTOR-BORNE INFECTIOUS DISEASE

Although defined in different ways by different authors, emerging infectious diseases can be defined as *a disease process for which a novel infectious agent has been discovered within the past 15 years or as the delineation of a newly discovered disease manifestation that can now be attributed to a previously known pathogen*. This definition has clinical, microbiological, and epidemiological utility. An example of a newly discovered genus of bacterial pathogens would include most of the *Bartonella* species that infect dogs or human beings, which have been discovered within the past 15 years.

VETERINARY MEDICINE AND VECTOR-BORNE INFECTIOUS DISEASE SURVEILLANCE

Unfortunately, a Center for Disease Control and Prevention for the investigation of vector-borne diseases of domestic or wild animals does not exist. Therefore, the veterinary profession lacks local, regional, and national incidence and prevalence data for most, if not all, companion animal and wildlife infectious diseases. As estimates indicate that 75% of the recently discovered emerging infectious diseases are zoonotic in nature, the importance of tracking infectious disease trends in companion animals and wildlife species is increasingly obvious to the medical and scientific communities.

As American households now have more dogs (estimated at 70 million) and more cats (estimated at 100 million) than any time in history, and because intimate contact between pets and their owners is greater than in previous generations, pet-associated diseases are being recognized with greater frequency. This is particularly true when pets are maintained by immunocompromised individuals. Fortunately, a reappraisal of human health care delivery has led to a renewed emphasis on comparative medicine, ecosystem health, and the concept of “one medicine.” As human medicine is devoted to the medical management of diseases in a single species, veterinary medicine must play an increasingly important role in ecosystem health, public health, and comparative infectious disease medicine.

Increased veterinary involvement will be particularly critical in zoonotic, vector-borne infectious diseases in the future. As domestic and wild animals experience substantially greater exposure to vector-borne organisms, animals can serve as natural reservoirs for human infection or as environmental sentinels for the detection of transmission of vector-borne illnesses in a geographic location.

THE FAMILY DOG AS A SENTINEL FOR EXPOSURE TO VECTOR-BORNE INFECTIONS

In veterinary practice, there is precedent for screening cats and dogs for chronic infectious diseases, such as feline leukemia virus, feline immunodeficiency virus, and *Dirofilaria immitus*. Fortunately, most currently available screening tests are both sensitive and specific, critical requirements for any widely used screening test. Information derived from a vector-borne pathogen screening process can be used for client education (keep retroviral-infected cats indoors to avoid transmission to other cats), future patient management decisions (retroviral-infected cats will more frequently develop opportunistic infections), and treatment recommendations (early detection and treatment of canine heartworm disease).

Therefore, clinicians electing to screen dogs for a tick-borne pathogen could use the information in a similar manner. Detection of antibodies, antigens, organisms, or DNA does not definitively prove causation in an individual patient (ie, dog, cat, or human being). As will always be the case, these data must be assessed in conjunction with the history, physical examination findings, other diagnostic test results, and the response of the animal to treatment. Failure to respond to treatment would support the possibility of concurrent infection, defective immune function, or a concurrent noninfectious illness.

ROCKY MOUNTAIN SPOTTED FEVER AS AN EMERGING INFECTIOUS DISEASE

Although first described in Montana in the early 1900s, Rocky Mountain spotted fever (RMSF) remains the most frequently reported fatal human tick-transmitted disease in North America, with annual mortality rates ranging from 5% to 10%. In the context of an emerging infectious disease, there is now strong epidemiologic evidence that a recent outbreak of fatal and nonfatal human RMSF occurred in Arizona, which was considered a non-endemic area of the United States.

In this outbreak, *Rickettsia rickettsii* was transmitted by *Rhiphicephalus sanguineus* (the brown dog tick), which was not previously considered a vector for *R. rickettsii* in North America. Historically, only *Dermacentor variabilis* (south and eastern United States), and *Dermacentor andersonii* (northwestern United States and Canada) were known to transmit *R. rickettsii* to dogs or humans in North America. *R. sanguineus* prefers to spend all three life cycle stages on a dog. When the environment is infested with large numbers of ticks or if dogs are removed from a tick-infested house, human blood is an acceptable alternative to the brown dog tick. In this setting, *R. rickettsii* can be transmitted to human beings.

In the context of morbidity, mortality, and severity of disease, RMSF is the most important tick-borne infection of dogs in the United States. When the diagnosis of RMSF is delayed, neurologic dysfunction (ataxia, hyperesthesia, vestibular abnormalities, and seizures) and a fatal outcome are more likely. In addition to a nearly identical disease course, the onset and duration of hematologic and biochemical abnormalities, such as thrombocytopenia, anemia, leukocytosis, and hypoproteinemia (due to vascular leakage of proteins), are very similar when dog and human infection data are compared. Early therapeutic intervention with tetracycline, doxycycline, or a fluoroquinolone is equally efficacious based on treatment of dogs experimentally infected with *R. rickettsii* in our laboratory. Unlike infection with *Ehrlichia* species, which infers no protective immunity, infection with *R. rickettsii* appears to induce long-lasting (up to 3 years in an experimental canine study) immunity in both dogs and people.

ANAPLASMOSIS AND EHRLICHIOSIS AS EMERGING VECTOR-BORNE INFECTIONS

Of comparative medical importance, cats, dogs, horses, humans, and other animal species can all be infected with the same *Anaplasma* (some of which were previously classified as *Ehrlichia* species) or *Ehrlichia* species. Ticks in endemic regions, including *Ixodes scapularis, Ixodes pacificus,* or *Ixodes ricinus* (Europe) transmit *Anaplasma phagocytophilum* to cats, dogs, horses and human beings.

Anaplasma phagocytophilum causes a very similar acute disease presentation in cats, dogs, horses, and human beings. California, Minnesota, Wisconsin, and several New England states (areas endemic for *I. scapularis* or *I. pacificus*) report a particularly high prevalence of infection, with disease reported most frequently in dogs, horses, and human beings. Fever, lethargy, and a reluctance to move, accompanied by lymphopenia, thrombocytopenia, elevated serum alkaline phosphatase and amylase, as well as hypoalbuminemia, are the most common clinical abnormalities reported in dogs. In the northeast and north central United States, acute disease occurs most frequently in the spring and fall months during the periods that nymphal and adult *Ixodes scapularis* ticks are most active.

To confirm a diagnosis of anaplasmosis, acute and convalescent serology is recommended to document seroconversion to *A. phagocytophilum* antigens in acutely ill, febrile, and thrombocytopenic cats, dogs or horses. Active infection with *A. phagocytophilum* can also be confirmed by PCR amplification of organism-specific DNA sequences. Therapeutically, tetracycline hydrochloride or doxycycline elicits rapid improvement. Currently it is not known whether a dog, after immunologic or therapeutic elimination of an initial *A. phagocytophilum* infection, can be re-infected by homologous or heterologous challenge following exposure to additional *A. phagocytophilum*–infected ticks.

Compared with RMSF, death is a less frequent outcome in people infected with *E. chaffeensis, E. ewingii,* or *A. phagocytophilum*, although mortality rates have approached 5% in some studies. These infections can be particularly severe in elderly or immunocompromised individuals. Neurologic dysfunction, including visual disturbances, ataxia, tremors, seizures, and stupor, have been reported in both canine and human ehrlichiosis.

Current diagnostic modalities that detect antibodies to *E. canis* in serum samples, such as the microimmunofluorescent assay (IFA) or specific peptide ELISA assays, do not differentiate between infecting *Ehrlichia* species. Species determination is more important from a public health and disease prevention perspective than from a therapeutic perspective, as tetracycline derivatives appear to be effective for the elimination of all *Ehrlichia* species that infect dogs or people. Recent studies indicate that treatment with imidocarb diproprionate or enrofloxacin does not eliminate *E. canis* infection in dogs.

The *E. canis* genogroup contains three species that are known to infect dogs and people: *E. canis, E. ewingii,* and *E. chaffeensis.* The pathogenicity of these species in dogs has been established through the study of both natural and experimental infections. Dogs infected with *E. ewingii* will often have polyarthritis and at our institution are frequently referred to the Neurology Service. We and others have documented *E. chaffeensis* infection in dogs that is clinically and serologically indistinguishable from *E. canis* or *E. ewingii* infection. Due to frequent re-exposure to infected *Amblyomma americanum* ticks in endemic localities, re-infection with *E. chaffeensis* is likely.

BARTONELLA SPECIES AS EMERGING PATHOGENS IN DOGS AND PEOPLE

The genus *Bartonella* is currently comprised of 22 species and subspecies of vector-transmitted, fastidious, gram-negative bacteria that are highly adapted to one or more mammalian reservoir hosts. Recent reports have provided additional evidence for an intra-erythrocytic and endothelial localization of *Bartonella*, which provides a unique strategy for bacterial persistence. Although infection with *Bartonella* has been associated with a wide spectrum of human pathology, the most thoroughly characterized are: cat scratch disease and endocarditis in adults, febrile illness and granulomatous hepatitis and splenitis in children, and bacillary angiomatosis and peliosis hepatitis in immunocompromised individuals.

Bartonella vinsonii subspecies *berkhoffii* and *B. henselae* appear to cause similar disease manifestations in dogs. In seemingly healthy reservoir hosts (rodents and other small wild mammals, cats, and ruminants), *Bartonella* usually cause a long-lasting (months to years) intra-erythrocytic bacteremia, which can frequently be detected by lysis centrifugation or freeze-thaw blood culture and by conventional or real-time PCR (RT-PCR). Cats, which become infected as a result of flea infestation, are the major reservoir for *B. henselae*, whereas canines, including dogs, foxes, and coyotes, are the recognized reservoir hosts for *B. vinsonii (berkhoffii).* Although tick, and potentially flea transmission is suspected, the mode of transmission of *Bartonella* species to dogs is unknown.

THE VETERINARIAN'S ROLE IN DIAGNOSIS, TREATMENT, PREVENTION, AND PUBLIC HEALTH AS IT RELATES TO VECTOR-BORNE INFECTIONS

In addition to the historical role as providers of diagnostic, treatment, and preventive strategies for companion animal infectious diseases, today's veterinarians must assume an expanded role in the public health arena, particularly as it relates to emerging vector-borne infectious diseases.

Already, routine treatment of intestinal parasites in dogs prevents children from developing cutaneous larval migrans and visceral larval migrans, due to ancylostomosis and toxocarosis, respectively. To further guard against zoonotic diseases associated with intestinal parasites, veterinarians should educate pet owners on the importance of year-round prevention, as well as environmental control, including removing pet feces from the yard, covering sandboxes and discouraging raccoon latrines.

In a limited number of studies, the use of acaricides prevented transmission of selected tick-borne pathogens. Routine, year-round use of acaricides most likely decreases the transmission of flea and tick-transmitted pathogens, which may prevent anaplasmosis, bartonellosis, ehrlichiosis, Lyme disease, and RMSF in pets and their owners. Environmental control solutions, such as the use of insect growth regulators, can also help curb repeated flea infestations. In addition, veterinarians can protect pets and humans by counseling owners to keep lawns trimmed, remove brush piles, keep dogs on-leash to prevent them from brushing against vegetation in the woods, and carefully examine all family members, including pets, when returning from walks. More detailed information about controlling current and emerging zoonotic and vector-borne diseases is outlined in the Companion Animal Parasite Council (CAPC) guidelines.

On a daily basis, behavioral and environmental changes continue to alter the dynamics of vector borne infectious diseases in the United States and throughout the world. Veterinary clinicians are on the front lines of the battle to prevent, diagnose and treat vector-borne infectious diseases.

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BARTONELLOSIS: LEGAL AND MEDICAL IMPLICATIONS FOR VETERINARIANS

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The genus *Bartonella* is currently comprised of at least 22 species and subspecies of vector-transmitted, fastidious, gram-negative bacteria that are highly adapted to one or more mammalian reservoir hosts. Recent reports have provided additional evidence supporting intra-erythrocytic and endothelial localization of *Bartonella*, which provides a potentially unique strategy for bacterial persistence. Kempf and colleagues have also demonstrated in vitro infection of human CD34+ progenitor cells with *B. henselae*. Following infection of isolated human progenitor cells, intracellular CD34+ *B. henselae* numbers increased over a 13-day incubation period and bacteria were detectable in differentiated erythrocytes on days 9 and 13. Infection of progenitor cells followed by nonhemolytic intracellular colonization of erythrocytes would preserve the organisms for efficient vector transmission, protect *Bartonella* from the host immune response, facilitate widespread vascular dispersion, and potentially contribute to decreased antimicrobial efficacy.

BARTONELLA TRANSMISSION

Based upon recent research observations, the clinical and diagnostic challenges posed by *Bartonella* transmission in nature may be much more complex than is currently appreciated in either human or veterinary medicine. As reviewed in several publications, numerous domestic and wild animals, including bovine, canine, feline, human, and rodent species can serve as chronically infected reservoir hosts for various *Bartonella* species. In addition to the large number of documented reservoir hosts, an increasing number of arthropod vectors, including biting flies, fleas, deer keds, lice, sandflies and potentially ticks have been implicated in the transmission of *Bartonella* species.

In general, persistent bacteremia in a reservoir host does not induce obvious signs of disease or pathology. However, when a *Bartonella* species is transmitted from a reservoir host (a seemingly well adapted association) to a non-reservoir host (a poorly adapted association) by a cat scratch, an animal bite or by an arthropod vector, infection can induce diverse spectrum of clinical and pathological abnormalities. In people, *Bartonella*-induced disease manifestations can include fever of unknown origin, endocarditis, lymphadenopathy (cat scratch disease), granulomatous hepatitis, encephalitis and bacillary angiomatosis and peliosis hepatis, particularly in immunocompromised individuals. Although not previously reported to our knowledge, our research group has recently described putative bite transmission of *Bartonella quintana* from a feral barn cat to a woman. Dog and cat bites are a frequent cause of emergency room presentations in the United States and may well represent an under recognized source of *Bartonella* transmission to people. These and other recent findings emphasize the potential environmental complexity associated with putative *Bartonella* bite transmission.

CATS AS A RESERVOIR

To date, four *Bartonella* species have been isolated from cats, including *B. henselae, B. clarridgeae, B. bovis* and *B. kohlerae*. Based upon well documented publications or recent research abstracts, it is possible that all four of these *Bartonella* species can be zoonotic pathogens. In addition to the frequent cat scratch transmission of *B. henselae* (cat scratch disease) and potentially *B. clarridgeae,* there is increasing evidence that cats may be involved in the transmission of *B. quintana* to people. Recently, *B. quintana* DNA was amplified from the dental pulp of a cat and from cat fleas (*Ctenocephalides felis*) in France. Prior to these reports, Dider Raoult's laboratory also described two middle-aged female patients that had chronic peripheral or mediastinal adenomegaly respectively, that were infected with *B quintana*. Both women had close contact with cats. Central nervous system infection with *B. quintana* was also documented in two males from the southeastern US, one of whom had experienced numerous scratches on the upper extremities by a kitten several weeks prior to the onset of seizures. *Bartonella quintana* was also implicated as the cause of seizures in an 11-year-old boy who had been scratched by a kitten a few weeks prior to admission. This child had no prior history of fever or lymphadenopathy. When tested by the CDC, both *B. quintana* and *B. henselae* reciprocal titers were 2048, but only *B. quintana* DNA was detected in a serum sample. The historical failure to isolate *B. quintana* from cats may reflect infrequent bacteremia or perhaps a lack of sensitivity of currently available culture techniques. The use of an optimized culture medium, as described below, should be considered in attempting to determine if *Bartonella* spp. infection is causing disease in a cat.

DOGS AS A RESERVOIR

The extent to which dogs might contribute to the transmission of a *Bartonella* species to a human being by way of a bite or scratch is currently unknown. Canines, including dogs, foxes and coyotes can serve as reservoirs for *Bartonella vinsonii* (*berkhoffii*). Recently, we described four distinct genotypes of *B. vinsonii* (*berkhoffii*), with types I, II and IV found in dogs, types I and II in coyotes and type III in gray foxes. To date, *B. vinsonii* (*berkhoffii)* has been isolated from only one reported case of human endocarditis in Europe. Currently, there are no other reports suggesting *B. vinsonii berkhoffii* transmission from dogs to people via a scratch or bite. However during the past year, both the Centers for Disease Control in Atlanta and the Intracellular Pathogens Laboratory at North Carolina State University have isolated *B vinsonii* (*berkhoffii*) from human blood samples. The route of transmission has not been clearly established in these individuals, as they all have a history of extensive animal and arthropod contact. Although there are only a few reports in the world literature implicating dogs in the transmission of *B. henselae* to people, we have detected *B. henselae* DNA in blood, lymph nodes and saliva from dogs. The extent to which dogs can serve as a reservoir host for *B. henselae* has not been established, but *B.henselae* seroreactivity in healthy and sick dogs in the southeastern US is much higher than *B. vinsonii* (*berkhoffii*) seroprevalences in comparable dog populations. In addition, we have recently detected infection with a *Bartonella* spp. in 18% of healthy Golden retrievers and in Golden retrievers with lymphoma. Similar to people, dogs can develop endocarditis and presumably other serious disease manifestations when infected with non-reservoir *Bartonella* species, including *B. clarridgeae, B. quintana* and *B. washoensis*. Other than two dogs with *B. quintana* endocarditis, one from North Carolina and the other from New Zealand, and one dog each with *B. clarridgeae* and *B.* washoensis endocarditis (both from California) there are no other reports of infection with these nonreservoir *Bartonella* species in dogs, making bite transmission of these species from a dog to a human less likely.

WILDLIFE RESERVOIRS

Bartonella species have been isolated from numerous wild terrestrial animals, including deer, fox, lions, rabbits, raccoons and numerous rodent species. Recently, we reported the first detection of a *Bartonella* species from the blood of a cetacean, the harbor porpoise (*Phocoena phocoena*). Of potential importance, this represents the first evidence of *B. henselae* infection in a non-terrestrial animal. In recent years, a series of emerging or re-emerging infection diseases with serious epizootic and/or zoonotic potential had been described in marine mammals. These infectious threats, which include morbilliviruses, brucellosis, toxoplasmosis, sarcocystosis, papillomavirus, and West Nile virus, seem linked to anthropogenic factors. As was the case for brucellosis, which was recognized as a marine mammal emerging disease in 1994, bartonellosis may prove to be an important emerging marine mammal infectious disease in the future. Currently, the geographic distribution, the mode of transmission, the reservoir potential and the pathogenicity of blood borne *Bartonella* species in porpoises is yet to be determined.

ISOLATION AND MOLECULAR DETECTION OF *BARTONELLA* SPECIES

Because conventional microbiological techniques lack sensitivity, bartonellosis is usually diagnosed by PCR amplification of organism specific DNA sequences and/or through serological testing. Recently, the development of a more sensitive isolation approach, using BAPGM (*Bartonella* alpha *Proteobacteria* growth medium) followed by real time PCR has greatly facilitated the molecular detection or isolation of *Bartonella* species from the blood of sick or healthy animals, including human beings. Obviously, the relative sensitivity of the diagnostic methods used to detect *Bartonella* species infection greatly influences an investigator's ability to establish disease causation. The use of recently optimized microbiological techniques has facilitated the recognition of blood-borne *Bartonella* spp. infections in dogs, horses, human beings and porpoises in our laboratory.

HUMAN HEALTH IMPLICATIONS

Based upon the annual increase in publications related to *Bartonella* infections in animals and people during the past decade, it is obvious that members of this genus are gaining increased international scrutiny by the medical and scientific communities. When examining data generated in specific populations of naturally exposed healthy or sick animals, it is important to recognize the exceptional evolutionary adaptation of these microorganisms, which are able to induce persistent blood-borne infections in both animals and people. This adaptation complicates efforts to define causation in association with intravascular *Bartonella* infection. Animals function as blood reservoirs for various *Bartonella* spp., a process that facilitates a continued transmission cycle via arthropod or animal bites or scratches. Animal contact, which in many instances occurs to a wide spectrum of domestic and wild animal species is an obvious consequence of the daily activities of veterinarians, veterinary technicians, animal health researchers, ranchers, wildlife biologists and many other individuals in our society. During the past year, our laboratory has documented *B. henselae* or *B. vinsonii* (*berkhoffii*) infection in blood samples from people with extensive arthropod and animal contact. The potential clinical relevance of detecting *Bartonella* spp. in the blood of people with occupational animal contact is yet to be determined. Despite frequent occupational exposure to animals, it is important to acknowledge that most veterinary professionals, ranchers and wildlife biologists participate in a diversity of outdoor recreational and occupational activities that also increase the opportunity for *Bartonella* transmission by biting arthropods.

LEGAL IMPLICATIONS

Veterinarians are responsible for the medical care and general well being of all of the animal species on this planet, except for *Homo sapiens*. In regard to zoonotic disease transmission, veterinarians play a pivotal role in the public health infrastructure of our nation. Additional prospective studies are necessary to characterize the risk of human *Bartonella* infection following a cat or dog bite and whether these infections are always self-limiting. Although part of the natural evolutionary history of *Bartonella* and mammals, the legal implications of *Bartonella* transmission from pets to people in our society may create complications as well as opportunities for the veterinary profession.

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MOLECULAR DIAGNOSIS OF INFECTIOUS DISEASES: THE GOOD, THE BAD, AND THE UGLY!

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One advantage of experience (in this case, a 30-year career as an academic internist) is the eventual realization that our collective efforts to manage illness in our patients have numerous limitations. There are obvious practical limitations, such as time, money, equipment and expertise (or the lack thereof), that confront clinicians and pathologists on a daily basis. However, there are somewhat less obvious limitations that relate to the sensitivity and specificity of diagnostic testing and the failure or inability to pursue unusual or unknown pathogens in our patients. Molecular diagnostic approaches have begun to facilitate a "modern day" revolution in our understanding of the interactions of multiple infectious agents, the complexity of disease expression induced by acute or chronic infection, and has resulted in the redefinition of "previously understood" diseases such as babesiosis and leishmaniasis. Although there is an increasing appreciation for the importance of co-infection or polymicrobial infection in animal and human diseases, there are considerable gaps in our current understanding of the interactions between viruses, bacteria, protozoa and fungi as interactive contributors to complex disease expression.[2,3]

MOLECULAR DIAGNOSIS – THE GOOD

Without question various molecular based tools have facilitated tremendous advances in diagnosis of infectious diseases. Polymerase chain reaction (PCR) amplification of organism-specific DNA sequences can be accomplished in a matter of hours and in most instances the detection of a PCR amplicon confirms active infection with a specific organism. This approach has distinct advantages over culture, which can require incubation times ranging from days, to weeks, to months depending on the organism. In most instances, approaches that provide rapid culture results select for only a few more easily grown organisms. Although serology or examination of the cell mediated immune response will remain an important component of infectious disease diagnosis, these tests identify evidence of immune recognition of a pathogen. Failure to confirm active infection, cross reactivity among various infectious agents and for an increasing number of infections (babesiosis, bartonellosis, leishmaniasis and others) the serological response to the organism may be minimal or nonexistent, despite chronic, active infection are limitations to the interpretation of serological test results in a given patient.

In some instances, the advent of PCR and DNA sequencing has allowed for the detection, characterization and at times reclassification of previously unknown or uncultured organisms. A few examples include:

1. **The contemporary discovery, rediscovery and reclassification of *Bartonella* species.** Historically, two members of this genus were classified as *Rochilamea* (*Bartonella bacilliformis*) and *Rickettsia* (*Rickettsia quintana* and subsequently *Rochilamea quintana*) species, respectively. Although the genus *Rochilamea* is extinct, a recently discovered *Bartonella* species has been named *Bartonella rochilamea* in honor of the historical contributions of Henrique da Rocha-Lima. In 1992, only two *Bartonella* species (*B. bacilliformis, B. quintana*) were known to exist, whereas now there are greater than 22 *Bartonella* species or subspecies.
2. **The reclassification of the *Hemobartonella* and *Eperythrozoon* in the genera *Mycoplasma*.** As with *Rochilamea*, the *Hemobartonella* and *Eperythrozoon* genera no longer exist, as these organisms were reclassified as *Mycoplasma* species on the basis of 16S rDNA sequence similarity. As hemotropic *Mycoplasma* species have not yet been cultured, epidemiologic, and diagnostic studies were limited to visualization of the organism. PCR amplification and sequencing have facilitated a molecular-based reclassification of these organisms. In addition, PCR targeting specific *Mycoplasma* gene sequences has allowed for the more sensitive detection of these organisms in the blood of healthy and sick cats and dogs. As a result, depending on the population studied, a large percentage of healthy or sick cats can harbor *M. hemofelis,* Candidatus *Mycoplasma haemominutum* or Candidatus *Mycoplasma turicensis.*
3. **The reclassification of *Ehrlichia equi* as *Anaplasma phagocytophilum*.** In the United States, *E. equi* was discovered and initially defined by clinicians and researchers at the University of California at Davis as an acute febrile illness of horses that is accompanied by edema and a mild degree of thrombocytopenia. Progressively over the next 20 years, *E. equi* was found to induce an acute febrile illness, accompanied by thrombocytopenia in cats, dogs and human beings. Based upon 16S rRNA gene sequences derived from *Anaplasma, Ehrlichia* and *Cowdria* species *E. equi* was reclassified as an *Anaplasma* species. Subsequently, it has been recognized that various *A. phagocytophilum* strains induce disease in cats, dogs, horses and people throughout the northern hemisphere.
4. **The reclassification of *Cowdria ruminantium* as *Ehrlichia ruminantium*.** Historically, *C. ruminantium*, the causative agent of heartwater disease in cattle, has been an economically devastating tickborne infectious disease throughout much of Africa and some Caribbean Islands where *Amblyomma variegatium* ticks were imported on cattle shipped from Africa. Based upon the 16 rDNA sequence, *C. ruminantium* was reclassified as an *Ehrlichia* species. With the advent of PCR and DNA sequencing, evidence of *E. ruminantium* was reported in dogs and HIV-infected people from

South Africa. Although somewhat scientifically astounding, this observation may make phylogenetic and biological sense as it is now known that several members of the genus *Ehrlichia*, including *E. canis, E. ewingii* and *E. chaffeensis,* can infect both dogs and people following transmission by a vector tick. Therefore, the use of more highly sensitive molecular-based detection assays has resulted in a breakdown of the perceived "species barrier" for several *Ehrlichia* species.

In some instances, the advent of PCR and DNA sequencing has allowed for the initial discovery (or rediscovery) of an entire genus of intravascular bacteria. A specific example includes the genus *Bartonella*:

1. In the United States *Bartonella* species were discovered in the early 1990s in association with efforts to characterize "unculturable," silver-staining bacteria observed in HIV-infected individuals with bacillary angiomatosis and peliosis hepatis. Using 16S rRNA eubacterial primers and DNA sequencing, Dr. David Relman at Stanford University amplified sequences from BA tissues that were most similar to *R. quintana* and a previously unreported DNA sequence, which proved to be *Bartonella henselae*. Subsequent research confirmed that all cases of vasoproliferative peliosis hepatitis are associated with *B. henselae* infection, whereas bacillary angiomatosis has been associated with the isolation or molecular detection of *B. quintana, B. henselae* and most recently *B. bovis*.
2. After *B. henselae* was successful isolated from the blood of an HIV-infected individual (*B. henselae* Houston I, ATCC type strain) it was determined that cats were the primary reservoir hosts from which this organism was transmitted to humans. *Bartonella henselae*, as opposed to *Afipia felis*, is now considered the primary if not the sole cause of human cat scratch disease. Infection in an immunosuppressed human population facilitated the initial recognition and molecular characterization of *Bartonella* species infection in the US. Although the subsequent discoveries in the area of *Bartonella* research are too numerous to mention, *B. quintana,* historically associated with wars, famines and deprivation was found to be present in the US for the first time in history. Our research group has subsequently described *B. quintana* infection in a cynomolgus monkey (*Macaca fascicularis*), in dogs with *B. quintana* endocarditis and in cats that putatively transmitted *B. quintana* to a woman by a bite. Detection of *Bartonella* species infections in human beings and cats also lead to the isolation of a novel *Bartonella* subspecies (*B. vinsonii* subsp. *berkhoffii*) from a dog with endocarditis.
3. During the past decade, an expanding number of *Bartonella* species (at least 22 species and subspecies) have been discovered in domestic and wild animals, which serve as the primary bacterial reservoirs from which *Bartonella* spp. are transmitted to human beings or to other non-host adapted animals via bites, scratches or following inoculation by a spectrum of arthropods (lice, fleas, sandflies, biting flies and potentially ticks). Cats, cows, dogs, mice, rabbits, rats and squirrels can experience chronic (months to years) blood-borne infections with host-adapted *Bartonella* species, with the potential for transmission by bites or scratches to people.
4. Our research group has emphasized studies that have resulted in the enhanced detection of *Bartonella* species in the blood of animals and humans using an optimized combined pre-enrichment culture medium and a highly sensitive PCR. Pre-enrichment culture followed by PCR amplification of bacterial specific genes has resulted in substantial improvement in the ability to detect *Bartonella* spp. in the blood of people or animals that have substantial arthropod exposure or occupational animal contact. By targeting multiple genes, we have also documented that dogs and people can be infected with more than one *Bartonella* species.
5. *Bartonella* species are now recognized as a cause of serious disease manifestations including arthritis, endocarditis, encephalitis, meningitis, hepatitis and lymphadenitis in dogs and people. It is very possible that these organisms represent an occupational risk for those individuals with extensive animal and arthropod exposure.[8,10]
6. As most *Bartonella* species have been discovered in the past decade, there is still much to learn regarding routes of transmission and disease causing potential. Recently, we have documented a high prevalence of *Bartonella* infection in the lymph nodes of healthy Golden retrievers and Golden retrievers with lymphoma. In this same study, we were unable to detect *Anaplasma* or *Ehrlichia* DNA in the blood or lymph nodes of the study population.

MOLECULAR DIAGNOSIS – THE BAD

The basis of all molecular diagnostic testing is a cumulative genomic data base (Gen Bank), which stores and provides DNA sequences for the public good. The source of the sequence, pending publications and other information relative to the deposited sequence is cited in the data base. Unfortunately, there is substantial variation in the length and quality of the deposited sequence and the data that is provided relative to the source of the sequence. Although by definition a molecular based diagnostic test should be 100% specific, based upon the premise that a unique gene sequence is being targeted, this is not always true or feasible for technical reasons. A few specific examples:

1. The 16S-23S intergenic spacer region has proven to be a valuable target for the molecular-based diagnosis of *Bartonella* species infection. For the genus *Bartonella,* there is in most instances substantial variation among species within the ITS region. Therefore, using the ITS region as a

molecular target would allow for both detection and speciation of the infecting *Bartonella* species in a single PCR reaction. When PCR primers were selected for this purpose by our laboratory and others, there *Mesorhizobium* (a plant-adapted bacteria that is phylogenetically related to the genus *Bartonella*), ITS sequences had not been deposited in Gen Bank. As would be expected, this plant bacteria is frequently found in water and unfortunately can contaminate molecular grade water resulting in a false positive diagnostic test result (amplification of *Mesorhizobium* DNA that is of the same amplicon size as a *Bartonella* species). In both our diagnostic (Vector Borne Diseases Diagnostic Laboratory) and research laboratories (Intracellular Pathogens Research Laboratory) we have a saying: **A band on a gel is only a band on a gel until a DNA sequence from that specific band is available for genus and species confirmation.** The advent of real-time (or quantitative PCR) with the use of melt curves has improved, but has not eliminated the potential for cross priming and misinterpretation of a PCR result.

2. Due to the available sequences and the relative high degree of genomic conservation among these species, most diagnostic laboratories target the 16S rRNA gene by PCR for the diagnosis of *Anaplasma* or *Ehrlichia* infection. In our laboratory a single PCR reaction is used to document infection with either species. If a positive genus PCR result is obtained, then five independent PCR reactions are used to determine if the patient is infected with *E. canis, E. chaffeensis, E. ewingii, A. phagocytophilum* or *A. platys*. This allows us to determine the infecting species, which has clinical, epidemiological and zoonotic implications and allows for the detection of co-infection with more than one *Anaplasma* and *Ehrlichia* species. Unfortunately, all bacteria are believed to have one or more 16S rRNA genes, most of which have been conserved in bacteria for millions of years. When a diagnostic test targets a gene that is highly conserved among numerous bacterial species, cross priming can result in multiple bands or bands of an appropriate size for the targeted organism because of contamination of molecular grade water, the Taq polymerase or the primers with bacterial DNA. Although a potentially valuable diagnostic tool, assays that nonspecifically target the 16S rRNA gene (ie, eubacterial primers) can be technically problematic for a number of reasons.

MOLECULAR DIAGNOSIS – THE UGLY

The international genome data base (Gen Bank) is available to anyone with computer access. Therefore, the sequences required for the design of a molecular diagnostic test are also available to anyone. Kits can be purchased for DNA extraction and thermocyclers used for PCR amplification are no longer cost prohibitive for many commercial laboratories. Unfortunately, technical expertise and rigid quality control is absolutely critical for the accurate performance of molecular diagnostic testing. There is no standardization or quality control testing among laboratories providing molecular diagnostic test results to the public. As is stated for other consumables, “Let the buyer beware!” In addition, many practicing veterinarians are not familiar with the strengths and limitations of this diagnostic approach, therefore assistance in the interpretation of both positive and negative test results is frequently required.

There are numerous other issues that complicate and challenge the current state of the art in molecular diagnostic testing. A few of these include:

1. An exceptionally well designed PCR assay that will reproducibly detect a low genome copy number (1–2 copies of an organism-specific gene target in a 50 μL PCR reaction) may not work as efficiently or may not work at all if transferred to a new (same manufacturer) or different thermocycler (different laboratory or different thermocycler manufacturer). Most importantly, different reagent quality, for example the source of Taq polymerase, can influence PCR sensitivity by 100- to 1000-fold.
2. PCR contamination is a constant fear for the Director of a molecular diagnostic laboratory. Unfortunately, despite appropriate controls, it is impossible to prove that a given PCR amplicon obtained from a patient sample is not a function of PCR contamination in the laboratory. Although a serious concern, the use of negative controls (extraction control, PCR control) in conjunction with laboratory surveillance greatly minimizes this concern. For technical reasons, the advent of real-time PCR has also minimized this concern.
3. With the use of samples such as paraffin blocks, specific protocols must be followed to avoid DNA carry over during the collection and extraction process, which has resulted in the reporting of false positive PCR results and data misinterpretation in the literature.

It is increasingly clear that the use of genomic approaches will continue to enhance our ability to diagnose and manage infectious diseases. The use of microarrays has already demonstrated utility for some diagnostic applications and testing on an array can facilitate the simultaneous detection of multiple RNA or DNA sequences (ie, multiple organisms) in a sample at the same time point. However, the sensitivity of microarrays may be less than optimal for detection of some infectious agents. Therefore, the validation process should incorporate the use of clinical samples to determine if detection by array is as sensitive as PCR amplification techniques. Efforts to detect bioterrorism agents will propel developmental efforts in molecular based diagnostic testing and will enhance the availability and utility of approaches that can be used for the evaluation of patient samples.

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CANINE LYME DISEASE – RECENT FINDINGS WITH IMPLICATIONS FOR PREVENTION AND TESTING

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Lyme disease is caused by transmission of *Borrelia* spp. spirochetes, including *B. burgdorferi* sensu stricto in the United States and *B. burgdorferi*, *B. garinii*, and *B. afzelii* in Europe, from infected *Ixodes* spp. ticks. As the ticks acquire a blood meal, the spirochetes travel to the salivary glands and are injected into the mammalian host, where they colonize adjacent tissues and establish a persistent infection despite a vigorous immune response.

Humans reliably develop acute symptoms that manifest most often as a flu-like illness characterized by an erythema migrans rash, and the patients possibly develop arthritis and/or cardiac or neurologic abnormalities. In contrast, dogs only occasionally develop acute illness.[1] Rather, the infection most often causes subclinical polyarthritis and/or periarteritis, only rarely progresses to frank recurrent arthritis with myalgia, fever, anorexia, and lethargy, and even less often manifests as renal failure, heart block, or neurologic disease. Moreover, the severity of the illness is influenced by the species and age of the dog. For example, beagle puppies are prone to oligoarthropathy, while adults more likely develop asymptomatic synovitis. In addition, Labrador Retrievers, Golden Retrievers, and Shetland Sheepdogs are susceptible to nephropathy from colonization of the kidneys. Despite the decreased severity of the clinical symptoms, however, the spirochetes persist for long periods of time in the skin and joint tissues, where they cause chronic inflammation characterized by focal infiltrations of primarily lymphocytes and plasma cells.[2] Additional studies to determine whether the inflammation becomes more significant as the dog's immune system becomes less effective remain an important, but as yet undetermined necessity.

Despite the differing clinical findings among humans and canines, both are unquestionably susceptible to infection, and the numbers of cases can be expected to increase with the increasing range and numbers of infected ticks. Moreover, the spirochetes may persist despite treatment with antibiotics.[3] While numerous studies have enhanced our understanding of human illness and reliable tests and effective treatments are the result, the volume of research in dogs has lagged considerably and additional studies are necessary before the same can be said for canine infection. Several recent findings, however, have highlighted strategies for more effective vaccination and more accurate tests.

EXPRESSION OF *B. BURGDORFERI* PROTEINS IN THE TICK AND IMPLICATIONS FOR VACCINATION

The persistence of the spirochetes and possibility of ineffective therapy led to the development of several dog Lyme disease vaccines that provide protection primarily by inducing the production of outer surface protein A (OspA) borreliacidal antibodies. The borreliacidal antibodies stimulate complement to form a membrane attack complex that kills the *B. burgdorferi* as the infected tick ingests blood. However, several shortcomings can cause the antibodies to fail. Most notably, the expression of OspA is down regulated immediately after the infected tick begins feeding, so the OspA borreliacidal antibodies are effective for only a short time period. In addition, OspA is antigenically distinct among *Borrelia* genospecies, so the antibodies are effective only against *B. burgdorferi* sensu stricto. Moreover, ticks are commonly infected with OspA$^-$ Lyme disease spirochetes.

Since the development of the existing commercial canine Lyme disease bacterins, researchers demonstrated that, in contrast to OspA, the spirochetes upregulate the expression of OspC immediately upon taking a blood meal,[4] and expression of OspC remains essential during the mammalian infection.[5] More significantly, a region at the carboxyl-terminus of OspC binds the borreliacidal OspC antibodies in human Lyme disease sera, and the epitope is conserved among the *Borrelia* genospecies.[6] The collective results therefore provide strong evidence that a vaccine that induces both OspA borreliacidal antibodies and OspC borreliacidal antibodies specific for the conserved epitope would provide more effective protection. More significantly, recent findings have provided the likelihood of significantly enhanced protection by using this type of new generation Lyme disease vaccine (Table 1).

Table 1. Detection of *B. burgdorferi* in adult female *I. scapularis* ticks after engorging on blood containing borreliacidal OspA antibodies, borreliacidal OspC antibodies, or both.

Blood	**No. ticks examined examined positive for *B. burgdorferi***	**No. (%)**
Normal	56	20 (36)
OspA	55	5 (9)
OspC	60	10 (17)
OspA/OspC	53	1 (2)

ANTIBODY RESPONSES AFTER INFECTION AND IMPLICATIONS FOR TESTING

Similar to human illness, *B. burgdorferi*-infected dogs develop a vigorous antibody response shortly after infection that includes opsonizing antibodies that mark the spirochetes for phagocytes and borreliacidal antibodies that stimulate formation of a membrane attack complex that kills the spirochetes independent of phagocytosis. However, there is little similarity between the specificity of the antibodies produced during human or canine infection (Figure 1), and the differences have important implications for serodiagnosis of Lyme disease in dogs.

Most significantly, the specificities of the antibodies produced during human illness are well characterized, and the result has been the development of several highly specific serodiagnostic tests that include a well-accepted Western blot criterion, a borreliacidal antibody test that shows promise as a "test of cure," and a C6 peptide ELISA that detects antibodies specific for a conserved region of an important surface (VlsE) protein. More importantly, the performances of the tests in the clinical setting have been or are being evaluated extensively.

In contrast, relatively few studies to characterize the antibody responses during canine Lyme disease have been performed. More commonly, tests developed for human illness have also been used for confirming the illness in dogs. In some instances, the test can provide reliable information. For example, detection of VlsE antibodies by the C6 ELISA provides highly specific confirmation of infection or exposure, and the test is not confounded by previous vaccination.[7] However, the test is insensitive during early infection (Table 2) and a positive result does not discriminate active infection. More significantly, results from other tests are almost certainly erroneous. For example, the criterion used for confirming canine illness by Western blot is irrelevant during canine infection (see Figure 1). In addition, the OspC borreliacidal antibodies that are a hallmark of human Lyme disease are detected only rarely during canine infection,[8] so tests that detect the response are also not useful. Additional research is therefore necessary before testing will be improved. However, recent findings highlight the potential for more accurate tests. For example, Jobe et al[8] showed that *B. burgdorferi*-infected dogs reliably (100%) produce antibodies specific for a 20 kDa protein, and the antibodies are not induced by vaccination. Additional studies to characterize the protein may therefore reveal a more accurate strategy for a canine test.

SUMMARY

The extensive volume of research concerning human Lyme disease has led to dramatic improvements in detection and treatment. In contrast, the clinical signs and symptoms of canine *B. burgdorferi* infection are significantly less conspicuous. Moreover, the antibody responses during canine illness have dramatic differences that negate the value of many well-accepted human tests. Recent research that has yielded additional information concerning protein expression by Lyme disease spirochetes in feeding ticks and antibody responses during canine illness that should result in improved vaccines and diagnostic tests.

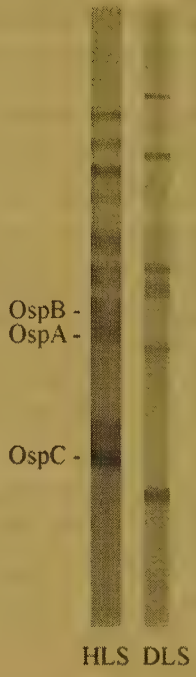

Figure 1. Western blot of typical human Lyme disease serum (HLS) and immune serum from *B. burgdorferi*-infected beagle (DLS). Reprinted with permission from Clinical Vaccine Immunology.

Table 2. Detection of C6-specific antibodies in immune sera from beagles infected[a] with *B. burgdorferi* (n = 14) for 40 or 100 days.

No. (%) immune sera positive[b] for C6-specific antibodies after:	
40 days	100 days
1 (7)	11 (79)

[a] Confirmed by recovery from skin biopsy.
[b] IDEXX SNAP 3Dx

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RATIONAL USE OF CANINE LYME VACCINES AND HOW TO IMPLEMENT A LYME DISEASE PROTOCOL

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Canine Lyme and the causative agent *Borrelia burgdorferi* have become a huge problem in many areas of the United States and Europe over the last 20 years. The dilemmas facing practitioners regarding this disease are typically related to how treat a clinical case of Lyme disease or even how to recognize infection with *Borrelia burgdorferi* in a sick dog. The questions most practitioners struggle with, more often are if, when and then how to monitor non-clinical dogs for evidence of *Borrelia burgdorferi* infection? And most of all how to prevent Lyme disease? How good is tick control? Should we or should we not vaccinate? Who should we vaccinate and do vaccines prevent or promote the most severe manifestation of Lyme disease – Lyme nephritis? After a brief overview of *Borrelia burgdorferi* pathogenesis necessary for the understanding of these issues this article will revolve around the ways that veterinarians can answer those questions best in their practice.

LYME DISEASE: CLINICAL SIGNS

The lack or apparent lack of clinical signs in most dogs with active Lyme infection makes both the diagnosis and the study of this disease very difficult. In dogs, clinical signs are observed only in approximately 10% of infected cases. These signs tend to occur 2 to 5 months after the infection and include lameness (mono- or polyarthritis), lymphadenopathy, lethargy, and fever. Skin lesions are uncommon in dogs. These signs typically resolve within approximately 3 days, in some case only with antibiotic therapy. Some questions remain regarding more serious, less common syndromes that have been associated with Lyme infection in dogs including renal disease (Lyme nephritis), cardiac disease (myocarditis), and neurologic disease. Another question yet to be answered is whether some dogs get the devastating chronic recurrent disease as seen in some infected humans.

DIAGNOSIS

What Diagnostic Tools are Available?

a. **Bacterial culture or identification.** This is very difficult in the case of Borrelia due to the small number of infecting organisms and the complicated techniques involved in their successful culturing

b. **Serology.** Clinically today we must rely on serology in conjunction with clinical signs to diagnose this disease. There are currently three types of serologic testing commercially available:

   a. Nonspecific ELISA. This is a very sensitive test aimed at identifying any antibodies produced against *Borrelia* whole cell antigen. It does NOT differentiate between antibodies produced in reaction to Lyme infection vs. Lyme vaccination and will be positive in both instances. Since we can usually never be sure of infection status and many times of vaccination status a positive non-specific ELISA should ideally be followed up with an additional test that would conform infection like a Western blot or a C_6 antibody test

   b. **C_6 antibody testing.** There are currently two commercially available tests for canine antibodies against the Lyme C_6 protein. This protein is expressed only during infection, therefore these tests are meant to be positive only in the event of natural exposure and negative in naive dogs or dogs vaccinated for Lyme. These tests include the in-house 3Dx or 4Dx SNAP tests and the quantitative C_6 antibody test available through IDEXX. Logical use of these tests:

      i. The SNAP 4Dx is an excellent test for screening dogs for Lyme infection. This can be done as part of a screening program for asymptomatic dogs or when Lyme disease is suspected. A positive result is indicative of active Lyme infection.

      ii. The quantitative C_6 antibody test tests for similar antibodies as the 4Dx but in a quantitative fashion. The value of knowing the quantitative C_6 titer is still unproven at this time, but we have shown that the titer correlated very well with circulating anti-Lyme immune complexes and is likely a very useful tool in treatment decisions of non-clinical dogs.

   c. **Western blot.** This technique involves a blot smeared with Lyme antigens located in known locations. This is a relatively expensive and labor intensive type of test and its interpretation requires expertise. Therefore this will never be in-house technology. As we have learned more about the 4Dx and quantitative C_6 assays, they have taken some of the role of the Western blot as a confirmatory assay. At this time I would recommend using the Western blot only in dogs where the vaccinal status is important to the veterinarian.

LYME PREVENTION

Tick removal: It takes time for an infected tick to transmit *Borrelia* to a dog, this typically can happen no sooner than 18 to 24 hours from the beginning of the blood meal. Therefore daily tick removal especially immediately after possible tick exposure is beneficial. People should handle possible infected ticks with care though, since there is the potential for transmission to the person from the tick. Tick control is probably one of the best ways to prevent Lyme disease. A recent study demonstrated that the use of tick control alone with fipronil was successful in preventing Lyme infection in most dogs when exposed to infected ticks compared to none in non-treated control dogs

Should We Vaccinate?

Whenever contemplating the use of a vaccine one needs to take weigh the pros and cons. These are the considerations that should be evaluated in such cases in my opinion:

How common is the pathogen? How common is the disease? How severe is the disease? How treatable is the disease? How good is the natural immunity? How expensive, reliable, and safe is the vaccine? Is there a zoonotic potential? Now all that has to be done is to answer the above questions for the vaccine we are considering.

1. Common? The disease is very common. Even though most dogs are asymptomatic the infection rate is so high in the Northeast that it is a very common disease. 10% clinical signs of 50% to 75% of the dogs in some areas is a lot!
2. Severity? Not that bad in most cases. What we do not know is the prevalence and significance of more severe syndromes such as Lyme nephritis and chronic recurrent disease.
3. Treatable? Pretty treatable in most cases in terms of eliminating clinical signs. But in many dogs we think based on experimental studies we never get rid of the bacteria even with antibiotic therapy. So maybe not that treatable. And then of course there is Lyme nephritis which at best seems very hard to treat.
4. Natural immunity? Not very good. Since the immune response appears to dampen over time. This is likely a result of the bacteria hiding themselves from the immune system by “hiding” in cartilage and down-regulating their immunogenic surface proteins.
5. How expensive, reliable, and safe is the vaccine? There are two kinds of commercially available vaccines. Both appear to be relatively inexpensive. One is a whole cell bacterin and the other a recombinant outer surface protein A (OspA) single antigen vaccine. There is very little published safety data. Both vaccines are approved for dogs and so had to go through safety testing. Both types of vaccine are likely to be effective. Studies performed at Cornell using the recombinant OspA (Merial) vaccine showed very high protection rates when challenged with infected ticks 1 month and 1 year after vaccination. Both vaccines actually work in a similar way. This is by providing the dog with antibodies against OspA. These antibodies work in the gut of the tick to bind the bacteria during the blood meal. Once the bacteria have reached the body of the dog then vaccinational antibodies (from either vaccine) are not effective as the surface proteins covering the bacteria change they enter the mammalian body. OspC is the main immunogenic protein exhibited by the tick in the dog’s body during natural infection.
6. Zoonosis? Not really, although there is some risk from infected ticks that are removed before finishing the blood meal. When given a choice the ticks tend to only feed on one species at a time.

The Safety of Lyme Vaccines

There are different aspects to this question:

1. Regarding acute vaccine reactions: Simplistically one could say: All the dogs in the vaccine studies seemed fine so the vaccine must be safe. Obviously that is not good enough. The vaccine studies are too small to pick up uncommon reactions, are too short in duration, are invariably conducted by the vaccine companies themselves and most of them are never published. There are actually also safety studies conducted on every vaccine that are much larger, but also typically looking for acute reactions and most often not published.
2. The more pressing question is: Do vaccines contribute to clinical signs associated with Lyme disease or to the syndrome known as Lyme nephritis? A large amount of new and exciting data will be presented to try to answer this question. And it is a good question because we now know that Lyme nephritis is not caused by an inflammatory response to renal invasion of *Borrelia burgdorferi* organisms. Lyme nephritis is a condition associated with an accumulation of immune complexes in the kidney. We have shown that all Lyme positive dogs have a measurable level of Lyme specific circulating immune complexes in their blood. More recently we have been able to purify renal immune complexes from kidneys of dogs that died of Lyme nephritis and to identify Lyme specific antibodies are present within those immune complexes. Studies are still ongoing regarding possible co-infections or other antigen-antibody complexes in those kidneys. Studies are also ongoing regarding the possible contribution of vaccination to circulating immune complexes. From very preliminary results we can say at this time that recombinant OspA vaccines do not appear to cause a major sustained increase in circulating serum Lyme specific immune complexes. Other evidence for the lack of a key role for vaccine induced antibodies in regards to Lyme nephritis is the fact that despite looking very closely we have yet to identify a dog with Lyme nephritis with solely vaccinal antibodies within the renal immune complexes. Vaccinal antibodies in the immune complexes are also pretty rare in dogs that have been infected as well as vaccinated against Lyme disease.

My Recommendations (based on the above criteria):

1. Vaccinate in endemic areas? Yes, to prevent infection from ticks. What defines an endemic area? That is a good question. Through screening the prevalence should be determined in each practice. In an area with high prevalence (over 20%?) It may be logical to vaccinate all dogs. In an area with less prevalence possibly identifying dogs at increased risk is the wise way to do it.
2. Vaccinate Lyme negative dogs? Yes.
3. Vaccinate positive dogs? Yes, to prevent reinfection from the tick as the immune system may or may not

be able to prevent active disease even if the dog is Lyme positive. Here is the most relevant place for the concern over the immune complex issue. Until the conclusion of the above studies based on what I know so to date that is my recommendation. In the future if the post vaccinal increase in circulating immune complex appears to have clinical significance it may need to be adjusted. Possibilities for adjustment of the recommendations include a course of treatment with doxycycline prior to vaccinating a positive dog, especially a dog with a high quantitative C6 titer, or choosing a recombinant vaccine vs. a whole cell bacterin when vaccinating a positive dog.

4. How often to vaccinate? Annually at this time with the currently available vaccines.
5. Even in vaccinated dogs TICK CONTROL must be stressed to the owners since a very heavy Lyme burden may override vaccinal protection.

LYME TREATMENT

I believe there is little question about treating Lyme positive dogs with clinical signs. What should we use? There is no proven benefit in vaccinating a dog with clinical Lyme disease from a therapeutic standpoint. So we are left with antibiotics. Amoxicillin and doxycycline both work well although there is some evidence that doxycycline may be better, and should be used for 4 to 6 weeks. Doxycycline will also likely be better at treating additional organisms that may have co-infected our patient along with Lyme disease. The harder question is what about the non-clinical majority. Why not treat them all? Although it is hard to look the concerned owner of a young Lyme positive Golden retriever in the eye and refuse to treat a possibly fatal disease, theoretically we should approach the treatment question from a risk-cost-benefit standpoint. At this time I am not sure we have enough information to make an informed choice in this matter. What do we know?

1. Lyme positive dogs may remain infected with Lyme at low numbers with or without treatment.
2. There is some evidence to show that in many cases treatment tends to lower Lyme titers faster than they would decline without treatment. This may be true for bacterial load as well as serologic titers.
3. Based on experimental and a growing number of field studies data Idexx laboratories is currently recommending treatment above a certain C_6 quantitative titer and then rechecking titers 6 months later to evaluate treatment afterwards. As we gain experience with this approach and controlled field studies are published we will have a clearer understanding of the question to treat or not to treat?

LYME NEPHRITIS

Current Recommendations for Screening and Treatment of Dogs with Suspected Lyme Nephritis

(These are based on limited experience, theory and not yet on strong clinical data!).

1. Monitor dogs in endemic areas for Lyme infection
2. Screen all positive dogs for signs of proteinuria or microalbuminuria.
3. Screen all dogs that present with proteinuria or microalbuminuria for Lyme.
4. Consider treating any dogs positive for both Lyme and proteinuria or microalbuminuria with 4-6 weeks of doxycycline.
5. If proteinuria persists or worsens (based on urine protein/creatinine ratio):
   - Continue doxycycline
   - Consider low protein diet and an ACE inhibitor
   - Consider renal biopsy
6. If the renal biopsy is consistent with immune mediated GN consider immunosuppression with drugs like mycophenalate, azathioprine, chlorambucil, or cyclosporine.

References are available from the author upon request.

POTENTIALS AND PITFALLS OF INFECTIOUS DISEASE CONTROL FOR THE PRACTICING VETERINARIAN

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Clearly, the last thing we want as veterinarians is for our patients to go home sicker than when they came to us, especially with a disease acquired during a veterinary visit. A well-crafted plan is needed to guard against such disasters. When choosing a disinfectant, we must consider the spectrum of effect; method of delivery; constraints against efficacy (such as presence of organic matter); time to effect; and periodic verification that the disinfection program is working as intended. We need to consider numerous aspects of disinfection: hands, surfaces, cages, clothing, and the role of other animals all must be addressed.

SO, WHAT DISINFECTANT SHOULD BE USED?

There is no simple answer to this question. If you have only one disinfectant on hand, chances are it is not sufficient for all the circumstances you are likely to encounter. Factors to consider include the spectrum of effect; activity in the face of organic matter; whether or not it has detergent activity (functions as a cleaner as well as a disinfectant); speed of action; method of application; cost and safety. As with choosing an antibiotic, scientific research should be consulted as well as claims of manufacturers or venders.

Unenveloped viruses are among the most common and challenging small animal pathogens requiring our attention. Unfortunately, the quaternary ammonium disinfectants, which are among the most commonly used in veterinary medicine, have repeatedly been show to be incompletely effective against this class of viruses by independent studies—in spite of label claims to the contrary. Even the mighty bleach is not without its flaws. Although reliably effective against the unenveloped viruses when correctly applied, it has no cleaning properties whatsoever and is significantly inactivated by organic matter. Application of bleach to a contaminated surface is unlikely to have the desired effect. Although stable when stored in light-proof containers for at least 30 days, heat and exposure to light can substantially compromise the disinfectant properties of bleach solutions. The quaternary ammonium compounds, in spite of their weak performance against unenveloped viruses, have strengths that contrast with many of bleach's weaknesses: they do have some ability to act as a cleaner as well as a disinfectant (depending on concentration and formulation); they have better—although not complete—activity in the face of organic matter; and they are relatively stable in solution. Another promising disinfectant is potassium peroxymonosulfate (eg, Trifectant®). This has been independently proven against the unenveloped parvo and caliciviruses[1] and has relatively good activity in the face of organic matter and some cleaning as well as disinfecting properties.

GETTING THE "DRUG" TO THE BUGS

The method of application is just as important as choice of disinfectant. When at all possible, mops and buckets should be avoided. For small cleaning jobs, bottles with "squirt tops" rather than spray tops are ideal to decrease the amount of disinfect aerosolized into the environment. Opaque containers should be used for bleach. All bottles should be labeled with the identity of the disinfectant; all required safety information; and the *date and initials of the person who made up the solution.* For larger cleaning jobs, hose-end foamers or built-in dispensing systems are preferred. Where use of a hose is impractical, a hand-held or back-pack style pesticide applicator can be used. If buckets MUST be used, contamination of the disinfectant can be minimized by rinsing the mop or other applicator in a clear water bucket between each application of disinfectant. Separate cleaning supplies should be used for each area to be cleaned.

Whatever disinfectant and method of application is used, one key decontamination step is *drying* the environment. Fatal bacterial pathogens have been cultured from pools of water lingering in kennels that had been completely cleaned and disinfected, and even from the disinfectant dispensing system itself in one shelter outbreak.

GETTING A HANDLE ON HANDS

Keeping hands clean is important for protection of human as well as animal health. There are basically three methods for managing hands: gloves; washing with soap and water; and hand sanitizers.

Gloves: Gloves are the most fool-proof choice for preventing germ transfer on hands. A change of gloves between every animal is indicated when handling animals that may be infected with particularly environmentally resistant germs; when a zoonotic infection is suspected; or during any outbreak of unknown disease.

Hand washing: It is true that proper hand washing has the significant advantage of removing even the most resistant pathogens. But it's surprisingly hard to wash hands correctly, and compliance may not be all one could wish for. Ineffective hand washing may actually be *less* helpful than correct use of a good hand sanitizer. According to the Center for Disease Control, proper hand washing technique consists of the following:

- Wet hands with warm running water
- Lather with soap
- Scrub all surfaces for a minimum of 20 seconds
- Rinse
- Thoroughly dry hands using two single use paper towels for 10 seconds each—if cloth towels are used, a fresh one must be used for each hand washing episode. Hands should be dried for 10 seconds on one area, then 10 seconds on a fresh area of the towel.

As with environmental decontamination, the drying step is especially important. Moisture on hands may actually facilitate pathogen survival and transfer. Clients and staff should have ready access to hand washing stations stocked with soap and paper towels at all times.

Hand sanitizers: The best hand sanitizers for veterinary use should contain 60% to 90% ethanol alcohol. Alcohol-free products should generally be avoided: in addition to being less reliable against calicivirus, some of these contain phenol (Triclosan®) or quaternary ammonium (benzylalkonium) compounds, which can be toxic to animals at too high a concentration. No hand sanitizer is effective against the most durable pathogens, such as the parvoviruses or ringworm.

ONE FOOT AT A TIME

In human health care, hands are the primary culprit in disease transmission. For those of us in veterinary medicine, it's not quite so simple. Our patients—especially dogs—often sit on the floor of the waiting or exam room. The way many dog runs are set up, caretakers must walk in and out for cleaning, carrying with them whatever happens to be on the soles of their shoes.

Luckily, if the basic environmental cleaning program is effective, the risk of transmitting disease via footwear is probably not all that high. While its true that some pathogens may get tracked into a room when staff enters to clean it, if the last step is application of a good disinfectant, whatever was tracked in will be inactivated. Foot sanitation should be a greater concern under a few special circumstances: before entering areas where vulnerable animals (puppies and kittens) are housed on the ground; when entering and exiting isolation areas where animals are being treated for conditions caused by particularly durable pathogens; and during an outbreak of unknown cause.

There are two general options to prevent disease transmission via footwear: footbaths or dedicated boots/shoe covers. The obvious advantage of foot baths is that they are much more convenient than special shoes or covers. Everyone entering a given area can easily step into a foot bath on their way in and out. The disadvantage of foot baths, however, is a big one: they just don't tend to work very well. All disinfectants require some amount of contact time for optimal effect, and this will not be achieved with a quick dip in a foot bath. Often disinfectant foot baths are not of sufficient depth or used in such a way as to remove gross organic matter contamination of shoes, further compromising efficacy. To maximize effectiveness of foot baths:

- Use a disinfectant that is reliably effective against the pathogens that are likely present and that has reasonable efficacy even when contaminated by organic matter
- Make sure the foot bath is deep enough to completely cover shoe treads
- Provide a stiff bristled brush to remove dirt caught in shoe treads
- Change foot baths at least daily or more often if visibly dirty

CLOTHING: BEYOND FASHION STATEMENTS

So now we've dealt with hands and feet, leaving us only with that troublesome expanse of clothing in between. Even in the human health care world disease transmission on clothing is a big concern. For instance, one study found potentially harmful pathogens present on almost half of doctors' neckties. Clothing-borne disease transmission is a very real concern in veterinary medicine as well. This risk of disease transmission on clothing is enhanced by our patient's propensity to shed hair onto our clothing—hair that is potentially coated with everything from the animal's saliva and environment.

One of the most important—and reasonably easy—infectious disease control procedures is to have staff change clothing or wear protective garments for "dirty" activities such as cleaning and treatment of sick animals. Spare scrub tops or protective smocks should be freely available and used whenever interacting with a potentially infectious or high risk animal (e.g. one which has just been purchased, adopted, or spent time in a boarding kennel).

Finally, we come to the matter of laundry. Good news here: the vast majority of the time, all that's required is washing in either a regular or commercial washing machine with hot water and bleach, and drying on heat cycle. No more bleach than the usual amount for a given size of washing machine is needed (half a cup for an average household washer). Although myths persist about bleach being inactivated by laundry detergent or hot water, this is not the case. As long ago as 1938, high-temperature laundering with bleach was found to be an effective method of sanitizing hospital linens, and subsequently it was found that bleach used with water temperatures as low as 48°C (118°F) was sufficient.

VERIFYING "CURE"

Occasionally reviewing the efficacy of a hospital disinfection program can be a powerful educational and motivational tool for staff. This does not have to be either punitive or costly. One simple method is to streak bacterial culture plates from cages, exam surfaces and scrub tops. A sterile environment is not expected, but comparison of culture numbers to a known "clean/disinfected" surface can be helpful. Alternately, products designed to mimic the spread of germs can be used.

PREVENTING ADVERSE EFFECTS

Disinfectants are not without the potential for harm. At minimum, use of disinfectants at excessively high concentrations can create respiratory irritation for animals and staff, and some chemicals (such as quaternary ammonium and phenol disinfectants) can actually be fatal when applied incorrectly.[10-12] A more subtle risk is the wasted time and money and false sense of security that comes with an ineffective program. *Disinfectants for veterinary use should be limited to those specifically tested and labeled for use in this setting.*

PUTTING IT IN WRITING

One of the most important and often-overlooked parts of any infection control program is to ensure training and compliance. I can't count the number of times I have visited a shelter or boarding kennel that seemed to have excellent procedures in theory, only to find that in reality the practice was quite different. This could be something as simple as loss of a measuring device to ensure the correct dilution of disinfectant. The process for disinfectant dilution and application should be clearly written out, posted, and periodically reviewed. Measurements should be clearly marked on containers as well as posted. Staff should be signed off after training, periodically re-evaluated, and all members of the veterinary team should be encouraged to reward good disinfection control behavior when they see it as well as report any problems.

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ACVIM LYME CONSENSUS AND UPDATE

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Several years have passed since the ACVIM Consensus Statement concerning the hot topic of canine Lyme disease was written. Recent studies help clarify answers to some questions, but other areas remain controversial and need more study. Due to lack of space in these NAVC 2008 Proceedings, the following should be read in conjunction with the previously published "ACVIM Small Animal Consensus Statement on Lyme Disease in Dogs: Diagnosis, Treatment, and Prevention." The questions below are numbered as in the ACVIM Consensus Statement. The update here includes additional information as referenced, as well as the personal opinion of this author, and does not necessarily represent a new ACVIM consensus.

QUESTION 3: HAS "LYME NEPHROPATHY" BEEN DEFINITELY ASSOCIATED WITH *BORRELIA BURGDORFERI* INFECTION OF DOGS?

There have been more studies done to help us answer this question. Researchers continue to find evidence that Lyme antigens are found in the immune-complexes deposited in the glomerulonephritic lesions in seropositive dogs with protein-losing nephropathy, that is, the so-called "Lyme nephropathy" or "Lyme nephritis" cases. Goldstein[2] is ready to confirm now that YES, Lyme nephropathy is definitely associated with *Borrelia burgdorferi* infection, circulating Lyme-specific immune complexes, and Lyme-specific antigen-antibody complex deposition in the glomeruli of affected dogs. Validation comes from sophisticated polymerase chain reaction (PCR), immunohistochemistry, and elution studies on kidneys taken from dogs with clinical data supporting the diagnosis of Lyme nephropathy. The findings are corroborated by independent researchers from different laboratories. It does not appear that live organisms are required for this disease, since special staining, cultures, and PCR techniques often fail to show whole spirochete organisms or even *Borrelia burgdorferi* DNA in the kidneys. Chou et al demonstrated that Lyme nephropathy is a sterile, immune-mediated disease with very little DNA found by PCR.[3] In that study, 84% of suspected cases had positive immunohistochemical staining of the kidney with rabbit antibodies directed against a number of Lyme antigens, including p83, p34 (ospB), and p31 (ospA).

Interestingly, some of the antigens found in the complexes, such as ospA and ospB, are antigens which are not usually expressed so much in early Lyme infection but possibly may be expressed during late, chronic, or carrier infections, when the organisms may show antigenic variation as they express their repertoire in order to avoid the host's immunity. Some of the antigens found in the complexes are those which are normally expressed by *Borrelia burgdorferi* when the organism is in the tick or when cultured in vitro. This finding may have ramifications when we consider whether to use vaccines which contain these antigens (see below, Question 21).

QUESTION 5: IS THE CAUSE OF "LYME NEPHROPATHY" KNOWN?

Although there is agreement by the researchers that Lyme nephropathy appears to be an immune-mediated phenomenon, does that mean that Lyme infection CAUSES Lyme nephropathy? I think it's still difficult to answer that question. The cause may be complicated. It could be that Lyme infection is primary and that Lyme antigens trigger the disease process in a genetically susceptible individual, or perhaps circulating Lyme antigen-antibody complexes are merely trapped in the glomeruli as "innocent bystanders," secondarily caught in an inflammatory or immune-mediated process stimulated by some other cause(s). Koch's postulates have not been completely satisfied because there is still no experimental model for Lyme nephropathy. Beagles experimentally infected with *Borrelia burgdorferi* do not get Lyme nephropathy.

Breed predisposition for Lyme nephropathy is seen in Labrador and Golden retrievers and Shelties (although other breeds can certainly get it). Luckily most Lyme-positive retrievers do not have proteinuria. Many dogs infected with Lyme disease have circulating immune complexes but not all dogs with circulating Lyme specific immune complexes will develop Lyme nephropathy. More study is needed to determine whether an immune dysregulation, hypersensitivity, inherent kidney abnormality, strain of *Borrelia burgdorferi* infection, genetic background, co-infections, or other co-factors may be necessary to cause a dog to get sick with Lyme nephropathy.

QUESTION 7: WHAT ARE THE OTHER DIFFERENTIAL DIAGNOSES OR CO-INFECTIONS IN DOGS SUSPECTED TO HAVE LYME DISEASE?

Our list of possible co-infections to consider has increased. Many tick-borne diseases are "stealth" pathogens, causing chronic carrier states that may go unrecognized, but which might contribute to immune-mediated phenomena such as polyarthropathy or glomerulonephritis. It appears that animals that are co-infected with more than one organism are more likely to become ill. See more about them in "Co-infections in Lyme Endemic Areas" and "Polyarthropathy, Cytopenias, and Proteinuria" in these NAVC 2008 Proceedings.

Beall et al[5] showed that based on serology, co-infection with *Anaplasma phagocytophilum* and *Borrelia burgdorferi* was more likely associated with illness in dogs compared with infection with either organism alone. In fact, there was no difference between seropositivity rates between healthy and sick dogs for either of these organisms alone, but there was a statistical difference between the seropositivity rate for healthy co-infected (23%) and sick co-infected (43%) dogs.

Diroff et al studied the seroprevalence in dogs for antibodies against *Bartonella* spp by Western blot in our

Lyme endemic region.[6] The seroprevalence in sick dogs (20.4%) was significantly higher than for healthy blood donor dogs (7.4%). The effect of *Bartonella* spp co-infections in Lyme positive dogs needs more study.

There are new *Babesia* spp discovered (both large and small types) in Lyme endemic areas that we may be missing if we don't do PCR testing (Birkenheuer, personal communication). Antibodies against these other organisms do not cross-react on the serologic tests for *B. canis* or *B. gibsoni* antibodies.

QUESTION 8: HOW IS CANINE LYME DISEASE DIAGNOSED?

It is still very difficult to prove that Lyme disease is the real cause of clinical signs. Speck et al agreed that Lyme disease is overdiagnosed. In approximately 40% of presumptive canine borreliosis cases, other lesions were eventually found to be responsible for the clinical signs.

QUESTION 18: SHOULD HEALTHY DOGS BE SCREENED FOR *BORRELIA BURGDORFERI* ANTIBODIES?

This is still controversial but I recommend healthy dogs be screened for all the reasons listed in Ref. 1. I recommend the new SNAP-4Dx (IDEXX) test rather than the SNAP-3Dx because it also tests for *Anaplasma* spp. antibodies. See "What to Do with Positive SNAP-4Dx Test Results" in these NAVC 2008 Proceedings.

QUESTION 21: WHAT ARE THE PROS AND CONS OF USING VACCINES AGAINST *BORRELIA BURGDORFERI* IN DOGS?

The ACVIM Consensus showed that most specialists are not recommending Lyme vaccines, even in Lyme endemic areas. I agree and recent research has not changed my opinion. Recently, Chou et al found positive immunohistochemical staining for Lyme antigens in the kidneys of dogs with Lyme nephropathy including antigens which are in both the bacterin and subunit types of Lyme vaccines (see Question 3 above).[3] I would not want to sensitize a dog to these antigens, lest it have a more intense immune-mediated response due to the anamnestic response when seeing the antigens again after boosters or by natural infection. Or if a dog is already Lyme-positive and genetically or otherwise predisposed to deposit Lyme-specific immune-complexes in its glomeruli already, I wouldn't want to add more antigen or stimulus for deposition by vaccinating.

Goldstein[2] is currently studying Lyme-specific circulating immune complexes (CIC) in Lyme positive and negative dogs, before and after vaccination with Lyme bacterin or subunit ospA vaccine. Lyme specific CIC transiently rise after vaccination with either vaccine type, and this rise in CIC is exaggerated and prolonged in dogs which are already Lyme-seropositive before vaccination (Goldstein, personal communication, ACVIM Forum 2007). More study is needed to see if these dogs become proteinuric or if any kidney damage occurs. In past studies, high concentrations of Lyme-specific CIC levels were associated with illness and correlated positively with clinical signs of Lyme disease.

QUESTION 23: HOW EFFECTIVE ARE LYME VACCINES?

Efficacy is still difficult to analyze since the diagnosis of Lyme disease is problematic, so post-vaccinal serology is sometimes considered. Recent work by Topfer and Straubinger tested Western blots and antibody levels after administering five different types of Lyme vaccines: LymeVax, a monovalent bacterin with adjuvant (Fort Dodge), ProLyme, a subunit ospA vaccine with adjuvant (Intervet), Recombitek Lyme, a non-adjuvanted subunit ospA vaccine (Merial), and two other vaccines not generally used in the USA.[9] They found that all produced anti-ospA antibody levels that peaked and then waned at about 4 months, reaching pre-vaccination levels by 10 months. ProLyme appeared to provide longer-lasting protection than the others (probably because of its adjuvant), and Recombitek produced lower antibodies that declined rapidly (probably because of the lack of adjuvant). They found very little ospC antibody production with those vaccines. The Schering-Plough vaccine (Galaxy-Lyme, bivalent bacterin, adjuvanted), which was not tested in the previous study, was shown in another study to induce both ospA and ospC antibodies. OspC antibodies may be helpful to protect the vertebrate during early Lyme infection; however there are at least 13 different *Borrelia burgdorferi* strains with unique ospC antigens[11] in North America. OspC antibodies would need to be strain-specific.

QUESTION 24: IF A LYME VACCINE IS GOING TO BE ADMINISTERED, WHAT IS A COMMON PROTOCOL?

Since antibody levels appear to peak and wane fairly rapidly after immunization, Topfer and Straubinger recently recommended a third inoculation either to be given 2 to 3 weeks after the second immunization to induce an elevated antibody response, or (they prefer) to give the third inoculation 4 to 6 months after the original two vaccines, to induce higher antibody levels at a time when their study animals showed very low antibody levels.[9] The study did not go into the following year, so we don't know if twice annual boostering would be necessary for the lifetime of the dog.

QUESTION 25: WHAT ADVERSE EFFECTS ARE ASSOCIATED WITH ADMINISTRATION OF LYME VACCINES?

Moore[12] found that Lyme vaccine (monovalent bacterin) caused more post-vaccinal adverse events than any other canine vaccine in the study, when used alone, even when compared with that of Leptospirosis vaccines, which have been notorious for causing side effects. The side effects may be due to the adjuvant or numerous antigens found in bacterins, including the pro-inflammatory ospA.

Realize that most dogs receiving Lyme vaccines don't get very sick. But neither do most dogs that get Lyme disease. I do worry about the ones that might be genetically predisposed to immune-mediated diseases triggered by Lyme antigens, so I still don't recommend Lyme vaccines. I recommend good tick control, which we need to use anyway in Lyme endemic areas because of all the other tick-borne infections we have.

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WHAT TO DO WITH POSITIVE SNAP-4DX (IDEXX) TEST RESULTS

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SHOULD WE USE SUCH A SCREENING TEST FOR HEALTHY DOGS?

Some veterinarians feel that since so many seemingly healthy dogs are asymptomatic carriers for borreliosis (Lyme), ehrlichiosis, and anaplasmosis and since current recommendations hold that asymptomatic carriers do not need to be treated, that there really is no reason to use such a screening panel on most dogs. Those clinicians may choose to do regular heartworm screening on normal dogs (which will not be discussed here), and they may save the SNAP-4Dx (IDEXX) test for dogs with clinical signs of one of those other diseases, (eg, polyarthropathy, vasculitis, lymphadenopathy, protein-losing nephropathy, cytopenias) when they suspect one of those infections may be causing trouble. But I recommend using the SNAP-4Dx as a routine tool. Knowing the seroprevalence for these diseases in your practice area will actually help you to avoid overdiagnosis and misdiagnosis, will improve your client education efforts concerning tick-borne diseases and tick control, will improve your "herd" health preventive management protocols especially where you know seroprevalence is high, and improve your ability to monitor the individual patient for occult proteinuria and other silent changes which may occur with these "stealth" diseases, before the animal becomes overtly ill.

POSITIVE LYME TEST RESULT

The SNAP-3Dx and SNAP-4Dx (IDEXX) tests screen for antibodies directed against natural exposure to *Borrelia burgdorferi*, the agent of Lyme disease. The tests utilize a synthetic C6 peptide as the antigen, which mimics the constant part of the VlsE antigen, which is only expressed by the *Borrelia burgdorferi* organism when it is in the host (in this case, the dog). Therefore, the test will not be positive due to antibodies directed against any of the available Lyme vaccine antigens, for instance the subunit vaccine's ospA antigen or, in Lyme bacterins, the antigens of *Borrelia burgdorferi* as they are expressed in the tick or in *in vitro* cultures of the bacteria before they are inactivated/killed for the production of bacterin. The C6 peptide IDEXX test is very sensitive and specific; it does not pick up antibodies against other spirochetes such as *Leptospira* spp or other *Borrelia* spp. Testing for acute and convalescent (paired) titers is not necessary since we know from experimentally infected dogs that by the time a dog would show clinical signs of Lyme disease, it should have seroconverted and show a positive test result.

Most dogs exposed to *Borrelia burgdorferi* remain healthy carriers and treatment is not necessarily warranted for all seropositive dogs. Deciding about treatment for an individual dog depends on whether the dog is showing signs of illness suggestive of Lyme disease (arthritis/fever, protein-losing nephropathy, or very rarely uveitis, carditis, etc.), whether it has occult signs suggestive of Lyme disease (proteinuria), and whether the owners and/or veterinarians involved are wanting to try to clear the dog of the carrier state, in the hopes that it might prevent future problems (although there is no clear evidence that such treatment will indeed clear the dog of the carrier status or that it will prevent future problems).

The IDEXX website recommends a two-tier approach, following up a qualitatively positive in-house SNAP-3Dx or SNAP-4Dx Lyme C6 antibody test result with a Lyme Quantitative C6 Antibody test (IDEXX Reference Laboratories). The website recommends using a cut-off of 30 U/mL, below which signs should probably not be attributed to Lyme disease, and above which treatment would be recommended. However, evidence is lacking that clinical signs correlate with the heighth of the Lyme Quantitative C6 Antibody test result, so asymptomatic dogs with high values do not necessarily need to be treated.

**Whether or not a dog becomes ill due to exposure, and whether or not a dog will be treated, when a dog is seropositive for Lyme natural exposure antibodies, the following recommendations hold:

- The dog should be screened and monitored for proteinuria
- The owners should be educated about the following:
    - Lyme disease in dogs versus humans (see references below)
    - Tick control, landscaping/tick avoidance, and tick prevention products
    - Public health regarding tick-borne diseases in their area
    - Public health regarding post-exposure prevention therapy in humans (200 mg doxycycline within 72 hours of pulling off an engorged *Ixodes* tick in a Lyme endemic area was shown to prevent Lyme disease in humans)
    - Possible co-infections and that seropositivity for Lyme antibodies is a marker for possible other exposures and carrier status.

Once a dog is positive on the SNAP-3Dx or SNAP-4Dx test for Lyme antibodies, it will probably remain so for years, whether or not it is treated or cleared, because the test is so sensitive, it may pick up very low antibody levels. So to check for any changes in antibody levels it is necessary to switch over to the Lyme Quantitative C6 Antibody test. I no longer recommend using other Lyme antibody tests, including the Lyme Western blot, KELA, total ELISA, or IFA tests.[2]

Symptomatic Lyme Positive Dog

Most dogs exposed to *Borrelia burgdorferi* remain healthy, but some do show signs of Lyme disease, including arthritis/anorexia/fever, polyarthropathy (especially including hocks and carpi), and more rarely, a serious immune-mediated protein-losing nephropathy (PLN), called Lyme nephritis or Lyme nephropathy, which appears to be triggered by exposure to Lyme antigens in dogs which may be genetically predisposed (usually Labradors, Golden retrievers, and Shelties). Lyme arthritis is generally self-limiting or quickly responsive to antibiotics, but canine Lyme nephropathy is a most serious form of Lyme disease and may not be responsive to therapy. Doxycycline is usually chosen since signs may be due to co-infections which may respond to doxycycline but not to penicillins. Also, doxycycline has anti-arthritic and anti-inflammatory properties separate from its antibiotic properties and has even been shown to help dogs with sterile cruciate rupture. Dogs with suspected Lyme arthritis should be checked for proteinuria. Early recognition and treatment of occult proteinuria, before clinical signs of hypertensive target organ damage, effusions/edema, thromboembolic events, or renal failure (vomiting, anorexia, weight loss, etc) is our best chance at decreasing immune-complex deposition and further damage to the kidneys.

I recommend that dogs which are Lyme-positive and have clinical signs suggestive of Lyme disease have the following done in addition to a complete history and physical examination:

- Screen for proteinuria by doing a full urinalysis with an ERD (HESKA) or microalbuminuria (MA) test, or a urine protein/creatinine ratio (see "Proteinuria: Don't Miss It" in these NAVC 2008 Proceedings). If proteinuria is found, monitoring, investigation, and intervention is recommended according to the ACVIM Consensus on Proteinuria. How often should the dog be rechecked for proteinuria if proteinuria is not initially found? Since screening for proteinuria is recommended for all dogs as part of their annual examination, at least annually, and perhaps more frequently in breeds predisposed to PLN.
- Submit Lyme Quantitative C6 Antibody Tests (pre- and 6-month post-treatment). If the pre-value is < 30 U/mL, consider other differentials causing the clinical signs. If the pre-value is greater than 30 U/mL, check for a decrease (50% or more) in the level 6 months after treatment. If infection has been chronic before treatment is initiated, the level may not decrease as much (because of immune memory), but the new baseline obtained may be useful to compare with future Quantitative results should clinical signs occur in the future, to determine if illness might be attributable to relapse/re-infection or not.
- Start Doxycycline, 10 mg/kg SID-BID for 1 month for arthritis or long-term for Lyme-PLN. If signs of arthritis/anorexia/fever or polyarthropathy do not respond within 24 hours, consider other differentials, such as immune-mediated polyarthropathy, etc. These cases often respond to corticosteroids.
- Client education about tick control and public health issues
- Consider testing for other tick-borne infections such as anaplasmosis, ehrlichiosis, bartonellosis, babesiosis, Rocky Mountain Spotted Fever (RMSF), mycoplasmosis, etc. (see "Co-infections in Lyme Endemic Areas" in these NAVC 2008 Proceedings).
- If proteinuria is found, consider further work-up including blood pressure measurements, serologic tests for co-infections, screening for other causes of proteinuria (infection, cancer, genetic predisposition, lupus, etc), possible renal biopsy, subsequent monitoring and treatment of proteinuria with an ACE (angtiotensin converting-enzyme) inhibitor such as enalapril or benazepril, diet modifications (eg, protein and phosphorus restriction), omega-3 fatty acid supplementation, an antithrombotic low dose of baby aspirin (0.5 mg/kg SID), possible immunosuppressive medication (pulse steroid/cytoxan or daily mycophenolate), and as necessary, antihypertensive medication such as amlodipine, colloids and/or crystalloid therapy, phosphate binders, and anti-emetics.

Asymptomatic Lyme Positive Dog

What to do with all those Lyme-positive asymptomatic dogs is still a hot controversial topic. I don't treat asymptomatic dogs (unless they have proteinuria) with doxycycline and I don't bother checking pre- and post-treatment Lyme Quantitative C6 Antibody tests, since I am not treating them and don't expect a decline in levels. The rest of the recommendations are the same as above.

The ACVIM Lyme Consensus statement did not recommend treating asymptomatic Lyme positive dogs. In some Lyme endemic areas, 70% to 90% of normal dogs are Lyme-positive and treating all those dogs is not warranted. Over-treating may cause side effects (anorexia, esophagitis, esophageal stricture) and bacterial resistance. Experimentally, adult Beagles seroconverted and had positive Lyme antibody tests, including elevated Lyme Quantitative C6 Antibody test results, but did not show signs of illness. Most Lyme-positive Labrador and Golden Retrievers (breeds most likely to get Lyme nephropathy) do not get sick with Lyme disease or show proteinuria (see "ACVIM Lyme Consensus and Update" in these NAVC 2008 Proceedings). Since the height of the quantitative titer may not predict whether or not a dog will become ill, doing Lyme Quantitative C6 Antibody tests are probably not necessary on asymptomatic Lyme-positive dogs. However, if the clinician plans to treat the dog (despite recommendations), testing pre- and 6 month post-treatment Quantitative C6 Antibody levels can be done to track any trend and to have a new baseline which will be available for comparison with future test results, should the dog ever become symptomatic.

POSITIVE *EHRLICHIA* OR *ANAPLASMA* SPP ANTIBODY TEST RESULT

The SNAP-3Dx and SNAP-4Dx tests screen for antibodies against *E. canis*. The test may pick up cross-reacting antibodies due to some other *Ehrlichia* spp infections, such as *E. chaffeensis*, but probably will miss antibodies directed against *E. ewingii* or *Anaplasma* spp (these may cross-react on *Ehrlichia* spp IFA tests). The SNAP-4Dx test also screens for antibodies against *Anaplasma phagocytophilum*, previously known as *Ehrlichia equi*, the agent of human granulocytic ehrlichiosis (HGE), and picks up the cross-reacting antibodies of *A. platys*, the agent of infectious cyclic thrombocytopenia. *A. platys* is mostly found in the southeastern states, and carriers are often asymptomatic or show intermittent thrombocytopenia which may not be clinically significant. If the *Ehrlichia* or *Anaplasma* SNAP test result is negative but signs suggest disease could be due to these agents, then paired (acute and convalescent) testing should be done, since the test may be negative in the acute stages of disease when antibody levels are still low and the dog has not had time yet to seroconvert. These tests are qualitatively positive or negative. If the clinician wants to check the height of a positive titer, there are laboratories which can do quantitative assays (eg, ProtaTek Reference Laboratory, Chandler, AZ or the NCSU Tick Borne Diagnostic Laboratory, Raleigh, NC). Circulating DNA of *Ehrlichia* and *Anaplasma* spp. can be tested and speciated by PCR technology (NCSU), using EDTA samples of whole blood. The best time to get a sample for PCR testing is before treatment (doxycycline) has been started, since the organisms may decrease in number in circulation and may hide in the reticuloendothelial system (spleen, bone marrow, etc).

Tick control, public health, and the possibility of co-infections should be discussed whenever a seropositive result is found (see above).

Once a dog is SNAP positive, it may remain positive for months to years, even after treatment. Comparing pre- and post-treatment quantitative titers may be helpful (6 to 12 months post-treatment) to check for possible clearance (decline) or to get a new baseline to compare in the future should signs recur (check for reinfection or relapse). I don't expect post-treatment titers to become negative; immune memory may allow for post-treatment titers to stay positive, but I watch for a decline. PCR testing may be helpful to check for the carrier state, but a negative PCR does not guarantee that the animal is completely cleared, since the organism may hide in the RES, and not exist in the small aliquot of circulating blood used for the test.

Symptomatic *Ehrlichia* or *Anaplasma* spp Positive Dog

Dogs with signs of Ehrlichiosis (bleeding, secondary bacterial infections, hyperviscosity syndrome, nephrotic syndrome, uveitis, polyarthropathy, CNS signs, etc.) may have laboratory changes on CBC (thrombocytopenia, anemia, and/or leukopenia), biochemical profile (hypoalbuminemia, hypercholesterolemia, hyper-globulinemia), urinalysis (proteinuria) and may have effusions, edema, uveitis, epistaxis or other petechial or ecchymotic bleeding, arthropathy, neurologic signs due to vasculitis, synovitis, plasmacytic meningitis, etc. Dogs with ehrlichiosis may even have a monoclonal gammopathy and/or bone marrow plasmacytosis, mimicking multiple myeloma.

Arthritis or polyarthropathy, fever, cytopenias (especially thrombocytopenia), and perhaps other signs have been attributed to *A. phagocytophilum* infection in dogs. CBC, Chemscreen, and urinalysis including screening tests for proteinuria, should be part of the diagnostic work-up. Buffy coat smears or joint tap cytology may reveal neutrophilic intracytoplasmic inclusion bodies (morulae).

All dogs with clinical signs suggestive of ehrlichiosis or anaplasmosis should be treated with at least a month's worth of doxycycline (10 mg/kg SID-BID) although they may not always be cleared of the carrier state. Dogs with leukopenia may have secondary bacterial infections, which may not be sensitive to doxycycline, and multiple antibiotics may be required, based on culture/sensitivity.

Quantitative titers taken pre- and 6-12 months post-treatment may be useful. Other (possibly paired) titers may be warranted, especially since signs of ehrlichiosis and anaplasmosis mimic each other as well as signs of RMSF, borreliosis, bartonellosis, etc. Since *E. ewingii* is not picked up by the SNAP test, IFA testing or *Ehrlichia* PCR (before treatment) may be done, especially in areas where *E. ewingii* is found (eg, Missouri). Animals which are co-infected with other tick-borne agents or other microbes may be more susceptible to showing signs of illness. *A. phagocytophilum* is transmitted by the same kind of *Ixodes* ticks that transmit Lyme disease, and in some Lyme endemic areas roughly 50% of Lyme positive dogs are co-infected. An association between seropositivity for antibodies against *Bartonella* spp and *Anaplasma* spp has also been noted.

Asymptomatic *Ehrlichia* or *Anaplasma* spp Positive Dog

The Ehrlichia Consensus Statement did not recommend treating asymptomatic dogs. However, I recommend CBC and urine testing to check for occult cytopenias and occult proteinuria. If the owners will allow an even more thorough follow-up, biochemical profile may reveal occult hypoalbuminemia, hyperglobulinemia, hypercholesterolemia, and renal evaluation (BUN, creatinine, phosphorus). If lab abnormalities are found, then the case should be handled as a symptomatic case, as well as have a more thorough diagnostic work-up to rule out other possible causes in the differential diagnosis list for the abnormality(ies) found.

It appears that many dogs are carriers of anaplasmosis without showing signs of illness. In addition to checking for proteinuria, a CBC may help pick up occult cytopenias (in which case, treatment is given).Treatment of asymptomatic dogs with normal blood and urine tests has not been advocated; it is unknown what treatment regime would clear them in any case. Experimentally, two weeks of doxycycline did not clear the carrier state; immunosuppression with prednisone unmasked these carriers as PCR positive once again.

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POLYARTHROPATHY, CYTOPENIAS, AND PROTEINURIA

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During second year in veterinary school, students may become frustrated as they realize that many of the canine diseases we teach about sound very similar as far as clinical signs, laboratory results, and even treatment. It's difficult to remember the details about how to differentiate the diseases. Interestingly, many tick-borne diseases mimic one another, even though the agents come from a variety of genera, transmitted by an assortment of tick types, and infect an array of cell types. In addition to confusion regarding their clinicopathologic differences and similarities, the student may realize that many, but not all, respond to doxycycline. As a member of the tetracycline family, this antibiotic can treat disease caused by intracellular organisms. In addition to its antibiotic properties, doxycycline has substantial anti-inflammatory activity, inhibiting osteoclasts and collagenase; in fact, dogs with sterile arthritis due to cruciate rupture have been shown to respond to doxycycline. Therefore response to doxycycline therapy may not prove that the diagnosis was correct, either for a particular organism causing infection or even if any infection at all was the cause of clinical signs.

Many of the tick-borne diseases mimic or trigger immune-mediated disease, and corticosteroids are often given along with doxycycline either initially or if response is not rapid with doxycycline alone. The antigens from these "stealth" organisms may be environmental triggers of immune-mediated disease or mimic auto-antigens, so immunosuppressive medications may be warranted, although these may not ultimately cure the individual if the underlying infection is not also treated. Some of the diseases cause carrier states, and it is not clear whether treatment sterilizes them or simply puts the individual in a premunitive state, able to cohabit peacefully with its parasite.

A group of target areas for inflammation are often seen together, including vasculitis, synovitis (polyarthropathy), glomerulonephritis (protein-losing nephropathy), uveitis and/or chorioretinitis, and sometimes meningitis. Positive anti-nuclear antibody and/or Coombs' test results, reactive lymphadenopathy, hepatosplenomegaly, and/or hyperglobulinemia may be seen. Bone marrow involvement may require bone marrow aspirate or biopsy, and some of the diseases may be confused with multiple myeloma, leukemia, blood cell dyscrasias, or immune-mediated hemolytic anemia. Animals with co-infections are more likely to show illness.

Below are charts of comparisons of some of these diseases that may help in the recognition of resemblances as well as divergences, to help differentiate, treat, prognosticate, and monitor these types of cases. For "tick panels" recommended in Lyme endemic areas for the commonly seen signs of polyarthropathy, thrombocytopenia, immune-mediated hemolytic anemia, and/or proteinuria, see "Co-infections in Lyme endemic areas" in these NAVC 2008 Proceedings.

	Agent	Type of Infected Cell	Major Vector	Tests other than Cytology	Need Paired Tests	Bite or Blood-borne	Rx	Carrier Status
Ap	Rickettsial	Granuloctye	Ixodes	ELISA PCR	X	X	D	X
Ay	Rickettsial	Platelet	Rhipi	PCR	X	X	D	X
Bar	Bacterial	Endothelial cells, Epi-rbc, Macrophages	Ixodes, fleas, other	PCR WB IFA culture	X	X	Z	X
Bb	Spirochete	Extracellular near fibroblasts	Ixodes	C6, WB ELISA IFA	No	Unlikely	D	X
Bc	Protozoan	Rbc	Rhipi	PCR IFA	X	X	Im	X
Bg	Protozoan	Rbc	Rhipi Bites	PCR IFA	X	X	Z/Qcfd	X
Bm	Protozoan	Rbc	Ixodes	PCR IFA	X	X	Z/Q	X
Bru	Bacterial	Lymphocyte Varied	Venereal Varied	RSAT ELISA PCR	X	X	MD	X
Cyt	Protozoan	Rbc, other	Derma	PCR	No	?	I	?(die)
Ec	Rickettsial	Monocytic wbc	Rhipi	ELISA IFA PCR	X	X	D	X

Ech	Rickettsial	Monocytic wbc	Ambly Derma	ELISA PCR	X	X	D	X
Ew	Rickettsial	Granulocyte	Ambly	PCR	X	X	D	X
Hep	Protozoan	Myocyte, Lymphoid, Liver, Wbc	Ambly (dog eats tick)	PCR Muscle biopsy	No		spc	X
Lei	Protozoan	Extracellular Macrophages	Sandfly	IFA PCR	No	X	PA	X
Lep	Spirochete	Extracellular	Urine	MA PCR	X	Unlikely	D	X
Myc	Bacterial	Epi-rbc	Fleas, Ticks	PCR	No	X	D	X
Rr	Rickettsial	Endothelial cells	Derma	IFA DFA	X	Unlikely	D	No

Consider looking for these diseases when presented with these signs:

	Lame	**↑Up/c or ↑BUN**	**Vasculitis or Epistaxis**	**Oculo-neural signs**	**RBC ↓**	**WBC ↓**	**Platelets ↓**	**Alb ↓**	**Glob ↑**
Ap	X	X	X	X	X	X	X	X	
Ay		?	?	?	X	X	X	?	
Bar	X	X	X	X	X	?	?	?	?
Bb	X	X	?	Rare			X if PLN	X	
Bc		X		X	X	Up	X	X	?
Bg		X			X	Up	X	?	?
Bm		X?			X?		X?	X?	?
Bru	X	X		X				X	X
Cyt					X	Varied	X	X	
Ec	X	X	X	X	X	X	X	X	X
Ech	X	X	X	X	X	X	X	X	X
Ew	X	X	X	X	X	X	X	X	X
Hep	Muscle	X			X	Up		X	X
Lei	X	X	X	X	X	X	X	X	X
Lep	Muscle	Tubular	X	X	X	Varied	Down	X	
Myc	?	?		X	X		X	?	?
Rr	X	X	X	X	X	X	X	X	Down

Abbreviations:

Ambly – *Amblyomma*
Ap – *Anaplasma phagocytophilum*
Ay – *Anaplasma platys*
Bar – *Bartonella* spp
Bb – *Borrelia burgdorferi* (Lyme disease)
Bc – *Babesia canis*
Bg – *Babesia gibsoni*
Bm – *Babesia microti*
Bru – *Brucella canis*
C6 – C6 peptide antigen in SNAP-3Dx, SNAP-4Dx or Lyme Quant C6 (IDEXX) tests
cfd – Clindamycin/Metronidazole (Flagyl)/Doxycycline combination
Cyt – *Cytauxzoon felis*
D – Doxycycline
Derma - *Dermacentor*
Ec – *Ehrlichia canis*
Ech – *Ehrlichia chaffeensis*
Ew – *Ehrlichia ewingii*
Hep – *Hepatazoon americanum*
Im – Imidocarb
Lei – Leishmaniasis
Lep – Leptospirosis
MA – Microagglutination test
MD – Minocycline and dihydrostreptomycin
Myc – *Mycoplasma* spp
PA – Pentostam (sodium stibogluconate), amphotericin B, allopurinol
Q – Atovaquone
Rhipi - *Rhipicephalus*
Rr – *Rickettsia rickettsii* (Rocky Mountain Spotted Fever, RMSF)
RSAT – Rapid slide agglutination test
Rx – Treatment
spc - Sulfas, pyrimethamine and clindamycin; decoquinate
Up/c – Urine protein/creatinine ratio
X - Yes
Z – Azithromycin (Zithromax)

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CO-INFECTIONS IN LYME ENDEMIC AREAS

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There are many tick-borne infectious agents in Lyme endemic areas besides *Borrelia burgdorferi* (the agent of Lyme disease), including the agents of anaplasmosis, ehrlichiosis, Rocky Mountain Spotted Fever (RMSF), babesiosis, bartonellosis, mycoplasmosis, and probably others. Since the availability of sensitive and specific in-house tests, namely, the SNAP-3Dx and SNAP-4Dx (IDEXX) tests, many dogs have been easily identified as seropositive for natural exposure antibodies directed against *Borrelia burgdorferi*. It is tempting to overdiagnose Lyme disease as the cause of almost any clinical sign. But consider that a positive Lyme test may just be a marker for tick and wildlife contact and the animal may have been exposed to a variety of organisms over time. Many of these organisms cause a carrier state with no apparent signs (referred to as "stealth pathogens") until the animal's premunitive (balanced) state has become compromised. The disease presentations may mimic each other as well as immune-mediated disease; indeed, some of these infections are associated with positive anti-nuclear antibody and/or Coombs' test results. Common signs include polyarthropathy (synovitis), vasculitis, cytopenias (anemia, leukopenia, and/or thrombocytopenia), proteinuria and protein-losing nephropathy (glomerulonephritis), uveitis/choroiditis, and/or sometimes meningitis. In experimental laboratory animals and in the field, co-infected individuals are more likely to show clinical signs of illness and to show anti-nuclear antibodies. When illness occurs in an animal which is a carrier, the clinical signs may be due to one or more of the infections, a newly acquired additional infection, a noninfectious process, or a combination of all these factors causing a shift in the delicate balance of immunoregulation in the individual. It may be a complete coincidence that the animal happens to be a carrier of one or more of these agents, since so many healthy animals are carriers, and the true cause of the clinical signs the animal presents with may be very difficult to identify.

This presentation will review tick-borne co-infections in Lyme endemic areas, and will not address other infectious diseases in the area that may mimic tick-borne diseases (eg, "inability to rise") such as leptospirosis, toxoplasmosis, and rabies. The term *Lyme endemic area* includes the 12 states with the highest Lyme incidence, responsible for 95% of the human cases according to the CDC. They are PA > NY > NJ > MA > CT > RI > WI > MD > MN > DE > VA > NH (in order of cases). Interactive maps showing canine infection rates (based on serology) in each state (and in each county) for heartworm, Ehrlichiosis, and Lyme disease are given at the website http://www.dogsandticks.com/maps/starthereMaps.html.

TICK PANELS FOR ASYMPTOMATIC DOGS

Although controversial, I do recommend screening healthy dogs with an annual SNAP-4Dx test. It helps me to know what the background seroprevalence is in our region with its tests for heartworm antigen and antibodies to Borreliosis (*B. burgdorferi*), Anaplasmosis (*A. phagocytophilum/A.platys*), and Ehrlichiosis (*E. canis/E. chaffeensis*). With this data I am better able to inform owners about public health issues and the importance of good tick control as well as checking/monitoring their pets for possible damage which these stealth organisms may cause. It is rewarding to identify occult proteinuria and/or cytopenia before the dog shows outward signs of illness, because early intervention may help ward off serious morbidity and mortality.

Exposure to the agent of Lyme disease is certainly common in dogs living in Lyme endemic areas. In some areas, 70% to 90% of all healthy as well as sick dogs are seropositive. Most seropositive dogs remain asymptomatic. For an update concerning Lyme disease in dogs see "ACVIM Lyme Consensus and Update" in these 2008 NAVC Proceedings.

A "guild" of organisms co-evolved and can be transmitted *by Ixodes scapularis* ticks, including *Borrelia burgdorferi*, *Anaplasma phagocytophilum* (previously known as *Ehrlichia equi*), *Babesia microti*, *Bartonella* spp, *Mycoplasma* spp, and rarely, tick-borne meningoencephalitis virus (a flavivirus). In some areas, up to 50% of Lyme-positive dogs are also seropositive for *A. phagocytophilum* antibodies. Dogs with co-infections are more likely to show illness. Since *A. phagocytophilum* can cause signs exactly like Lyme disease and since we rarely tested for it before the SNAP-4Dx test became available, many cases of *A. phagocytophilum* were probably attributed to Lyme disease in the past. Luckily, doxycycline would be the drug of choice for either infection.

I don't necessarily treat asymptomatic dogs that are found to be Lyme-positive. I monitor them for proteinuria with a urinalysis and ERD (HESKA), quantitative microalbuminuria test (MA, Antech) or a urine protein/creatinine ratio (see "Proteinuria: Don't Miss It" in these 2008 NAVC Proceedings) and I stress good tick control. Since Lyme seropositivity is a marker for tick exposure and the dog may be carrying other stealth pathogens, a tick panel including SNAP-4Dx (if not already done) and *Bartonella* Western Blot (see below) may be done if the owner intends to be very thorough. If the asymptomatic dog is seropositive for *Ehrlichia* or *Anaplasma* antibodies, in addition to monitoring for proteinuria, a CBC is recommended to check for any cytopenias. If cytopenia or proteinuria is found, a biochemical profile is recommended (to check for hypoalbuminemia, hyperglobulinemia, and increased kidney and/or liver values) and the dog is started on treatment including doxycycline. Finding proteinuria or a cytopenia means the dog is not really "asymptomatic." If proteinuria is found, it should be monitored, investigated, and if clinically appropriate, treated. Depending on the findings of the blood tests, more diagnostic tests may be warranted. Whenever I start doxycycline for a tick-borne disease, I like to get a pre- and 6 month post-treatment quantitative antibody titer for that infection. If the SNAP-4Dx test is positive and I am going to treat the dog, I follow it immediately with whichever quantitative titer is indicated, eg, a Lyme Quant C6 test (IDEXX), an *E. canis* titer (see below), or an *A. phagocytophilum* titer (see below) for my pre-treatment assessment. Then 6 months later I will repeat the titer and hope for a significant decline. Using the post-treatment result as my new baseline, if the dog should show signs of illness in the future, I can compare further quantitative results with the new baseline for evidence of relapse or reinfection. The qualitative SNAP test will probably remain positive for years and would not be as helpful to repeat in this situation, although in Lyme endemic areas we may do annual SNAP-4Dx testing to screen for antibodies to the other infections. More complete recommendations concerning what to do with asymptomatic as well as sick dogs that are positive for exposure and may be carriers for borreliosis, anaplasmosis or ehrlichiosis are presented in "What to Do with Positive SNAP-4Dx (IDEXX) Test Results" in these NAVC 2008 Proceedings.

TICK PANELS FOR SYMPTOMATIC DOGS

Sick dogs present a challenge for diagnosis, since many of these diseases mimic each other in clinical signs and many are treated with doxycycline or a combination of doxycycline and prednisone. Since doxycycline has anti-inflammatory properties, dogs may respond to Doxycycline even when they are not sick due to infection. For comparisons of the tick-borne diseases mentioned above and in regards to infectious agent, vector, transfusion risk, infected cell type, clinical signs, lab test abnormalities, diagnostic tests, treatment, and carrier status, see "Polyarthropathy, Cytopenias, and Proteinuria" in these NAVC 2008 Proceedings.

The following are some common disease entities and the tick-panels for diseases which might be considered for those signs in a Lyme endemic region.

Polyarthropathy

Tick Panel:

1. Lyme disease (SNAP-4Dx)
2. Anaplasmosis (SNAP-4Dx)
3. Ehrlichiosis (SNAP-4Dx)
4. RMSF (IFA at NCSU-VBDDL or ProtaTek Reference Laboratory, Chandler, AZ, see below).
5. Bartonellosis (Western blot at National Veterinary Laboratory; *B. henselae* and *B.vinsonii* IFA, cultures, or *Bartonella* spp. PCR - NCSU, see below)

If the dog is presented during the first 10 days or so of illness, do paired antibody titers (acute and convalescent) for anaplasmosis, ehrlichiosis, and RMSF since the animal may not have seroconverted yet and the acute test result may be negative. If the signs have been chronic (>3 weeks), you don't need to do a RMSF titer since RMSF does not cause a carrier state and would not cause chronic signs of illness. Other tests:

- Check for proteinuria (see above). If proteinuric, consider doing more diagnostic workup (blood pressure measurements, biochemical profile, imaging, biopsy) and consider prolonged treatment with doxycycline, angiotensin-converting enzyme inhibition, etc. If not proteinuric, continue to monitor.
- Consider doing a joint tap (you may see morulae of *Anaplasma* or *Ehrlichia* in white blood cells)
- If seropositive for a tick-borne disease other than RMSF, do pre- and 6 month post-treatment testing.
- Consider other differentials besides tick-borne diseases.

Immune-mediated Hemolytic Anemia, Thrombocytopenia, Leukopenia, and/or Proteinuria

Tick Panel:

1. Babesiosis (PCR, NCSU; *B. canis* and *B. gibsoni* IFA - NCSU or ProtaTek; *B. microti* IFA – ProtaTek) – anemia, thrombocytopenia, proteinuria
2. Lyme disease (SNAP-4Dx) – proteinuria
3. Anaplasmosis (SNAP-4Dx) – cytopenia, proteinuria
4. Ehrlichiosis (SNAP-4Dx) – cytopenia, proteinuria
5. RMSF (IFA at NCSU-VBDDL or ProtaTek, see below) – cytopenia, proteinuria
6. Bartonellosis (Western blot at National Veterinary Laboratory; *B. henselae* and *B.vinsonii* IFA, cultures, or *Bartonella spp.* PCR - NCSU, see below) – cytopenia, proteinuria
7. *Mycoplasma* spp. PCR (HESKA) – anemia

If the dog is presented during the first 10 days or so of illness, do paired antibody titers (acute and convalescent) for anaplasmosis, ehrlichiosis, RMSF, and babesiosis since the animal may not have seroconverted yet and the acute test result may be negative. If the signs have been chronic (>3 weeks), you probably don't need to do a RMSF titer since RMSF does not cause a carrier state and would not cause chronic signs of illness.

Other tests:

- Check for proteinuria (see above). If proteinuric, consider doing more diagnostic workup (blood pressure measurements, biochemical profile, imaging, biopsy, etc) and consider prolonged treatment[1] with doxycycline, angiotensin-converting enzyme inhibition, etc. If not proteinuric, continue to monitor.
- Lymph node aspirate, bone marrow aspirate, imaging, etc.
- If seropositive for a tick-borne disease other than RMSF, do pre- and 6 month post-treatment titers.
- Consider other differentials besides tick-borne diseases.

Ehrlichiosis, anaplasmosis, and RMSF infections may mimic one another. RMSF is more likely to cause neurologic signs than the others. Babesiosis infection may cause intravascular as well as extravascular hemolysis, and may cause significant thrombocytopenia even without causing significant anemia. Antibodies against *B. microti*, a small *Babesia* sp in Ixodid ticks in New England, Long Island (NY), and New Jersey, do not cross-react on serologic tests for *B. canis* or *B. gibsoni*, and perhaps we are missing finding it (*Babesia* PCR is recommended to check for any/all Babesia spp.). Novel unnamed *Babesia* spp. (both large and small types) have been found that may cause anemia and/or thrombocytopenia. A small *B. microti*-like organism (Theileria?) was noted to cause thrombocytopenia, azotemia, and protein-losing nephropathy in Spain. Antibodies to these different *Babesia* spp may not cross-react on the available *Babesia* serologic tests, so I now recommend that *Babesia* spp PCR be done.

Doxycycline is recommended to treat borreliosis, anaplasmosis, ehrlichiosis, RMSF, and mycoplasmosis. RMSF can also be treated with fluoroquinolones such as Baytril. Large *Babesia* spp infections are treated with imidocarb (Imizol) whereas small *Babesia* spp infections are treated with azithromycin/atovaquone (Zithromax/ Mepron) or a combination of clindamycin/ metronidazole/doxycycline (Antirobe/Flagyl/ Doxycycline). Bartonellosis is treated with azithromycin (Zithromax). All these organisms except RMSF can cause carrier states, and treatment may not clear them.

Breed Predispositions for Some Diseases in Lyme Endemic Areas

- Labrador and Golden Retrievers, Shelties: Lyme nephropathy
- Greyhounds: *Babesia canis* infections
- Pit Bulls and dogs which have fought with Pit Bulls: *Babesia gibsoni* infections
- Foxhounds: Leishmaniasis (not covered here)

DIAGNOSTIC TESTS

Antibody Titers (IFA or ELISA)

Thorough testing for exposure to multiple infectious agents certainly gets expensive, and if the animal presents during an acute phase of illness, convalescent (paired) titers are necessary to show seroconversion (from a negative to a positive result). IFA or ELISA titers can be qualitatively positive or negative, as in the SNAP-4Dx (IDEXX) in-house test for heartworm antigen and antibodies to Lyme, *Anaplasma* spp, or *Ehrlichia canis*, or more commonly, titer results are quantitative, for instance, the Lyme Quant C6 test (IDEXX Reference Laboratory), and *Ehrlichia canis*, *Anaplasma phagocytophilum*, RMSF, *Babesia canis*, *Babesia gibsoni*, *Babesia microti*, *Bartonella henselae*, *Bartonella vinsonii*. Many of these latter tests can be submitted to NCSU (Vector-borne Disease Diagnostic Lab, VBDDL, Raleigh, NC) or ProtaTek Reference Laboratory, Chandler, AZ.

Polymerase Chain Reaction (PCR)

PCR tests for microbial DNA are helpful especially in the acute phase of illness, before the animal seroconverts, and PCR is necessary to speciate the organism when multiple species in the genus may or may not cross-react on available serologic tests (eg, *Ehrlichia/Anaplasma* spp, *Babesia* spp, and *Bartonella* spp; submit to NCSU-VBDDL; expect a 4-week turnaround). For instance, the SNAP-4Dx test for *Anaplasma* spp does not differentiate between *A. phagocytophilum* and *A. platys* antibodies and the *E. canis* SNAP test probably picks up antibodies against *E. canis* and *E. chaffeensis*, but not those for *E. ewingii*. PCR for *Ehrlichia/Anaplasma* spp can help pick these up and differentiate (speciate) them. PCR for *Babesia* spp can pick up novel small (Theileria-like) and large (as yet un-named) *Babesia* spp present in Lyme endemic areas which do not cross-react with the serologic tests that check for antibodies against *B. canis* and *B. gibsoni*. PCR is the only test available (besides examination of blood smear cytology) for *Mycoplasma* spp (HESKA). Whole blood samples (in EDTA) are best collected for PCR testing before antibiotics are started since even one dose can decrease the numbers of circulating organisms, producing (false) negative PCR results. Weeks or months after treatment, PCR may be repeated to test for carrier status, although animals in a premunitive state may again have low numbers of organisms circulating but have organisms hiding sequestered in the spleen or reticuloendothelial system. Steroid administration or splenectomy may help unmask such occult carriers.

Western Blotting (WB)

There are many different *Bartonella* spp that we should look for and antibodies to them may not cross-react enough to be picked up by the available serologic tests for *B. henselae* and *B. vinsonii*. The *Bartonella* Western blot test (FeBart, National Veterinary Laboratory, Inc, Franklin Lakes, NJ) can be done with canine as well as feline serum and it helps detect banding patterns of antibodies present against *Bartonella* antigens.

The Western blot test for *Borrelia burgdorferi* antibodies used to be helpful after IFA or whole-cell ELISA (as a second tier test) to differentiate natural exposure versus vaccine-induced antibodies. Newer technology using the C6 peptide as antigen in the SNAP-3Dx, SNAP-4Dx, and Lyme Quant C6 tests (IDEXX) has made the Western blot test unnecessary. As a research tool, the Lyme Western blot needs more study to see if certain banding patterns might be associated with specific clinical signs.

Other Tests

Culture techniques for *Bartonella* spp. have recently become more sophisticated (NCSU), but there is still an 8 week turnaround. Direct fluorescent antibody testing on skin biopsies can be done for RMSF.

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TOP EIGHT QUESTIONS ABOUT VIRULENT HEMORRHAGIC FELINE CALICIVIRUS

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Feline calicivirus (FCV) is best known for its role in causing acute upper respiratory disease and oral ulceration in kittens and cats. Although morbidity in routine respiratory infections is high, these infections are rarely fatal. Most recovered kittens do develop a chronic carrier state characterized by continuous shedding of virulent virus from the oral cavity and respiratory tract that may last for months to years. The caliciviruses are comprised of a variety of small, non-enveloped, single-stranded RNA viruses that are regarded as being somewhat more resistant than feline herpesvirus-1 when outside the host. Unlike herpesvirus-1, however, over 40 strains of calicivirus have been identified and are known to vary significantly in virulence and antigenicity. Despite widespread vaccination against FHV-1 and FCV, these viruses are still known to occur in large numbers in the domestic cat population, particularly in multiple-cat households and animal shelters.

Since 1998, however, at least six outbreaks of a virulent feline calicivirus have been reported in the US. In these outbreaks, virulent, systemic strains of feline calicivirus (referred to as VS-FCV or hemorrhagic feline calicivirus) were recovered. Unlike FCV associated with routine, acute upper respiratory infection in kittens, infection with a virulent systemic strain of calicivirus has resulted in high mortality among previously healthy kittens and cats. Associated clinical signs include high fever, oculonasal discharge, alopecia, cutaneous ulcers involving the face and limbs, and subcutaneous edema. Infection causes epithelial cell cytolysis and systemic vascular compromise in susceptible cats. VS-FCV viruses appear to be highly contagious and are easily transmitted to other cats by way of eating utensils, hands, and even clothing.

Although the incidence of infection is quite low within the cat population, new vaccines are being developed to protect cats against the emerging strains of virulent FCV. This Q&A will look at the clinical aspects of hemorrhagic feline calicivirus and will facilitate decisions regarding the use of these new vaccines.

WHAT IS VIRULENT SYSTEMIC FELINE CALICIVIRUS?

Virulent systemic calicivirus is a newly recognized feline calicivirus variant that causes severe systemic disease with up to 60% mortality in affected populations of cats. Clinical signs include upper respiratory disease (oculonasal discharge, oral ulcers), pneumonia, peripheral edema and skin sloughing (especially on the face and limbs) due to cutaneous vasculitis, and systemic vasculitis with DIC that causes multiple organ/system failure which may lead to death.

WHICH CATS ARE MOST LIKELY TO BE AFFECTED?

Virulent systemic calicivirus has occurred almost exclusively in populations of group-housed cats. In each documented outbreak, the disease seems to have spontaneously appeared in the population, most likely by mutation from caliciviruses already circulating in the group of cats. This is supported by genomic analysis of the virulent strains -they are unique, rather than clonal, and have no common mutations that could easily explain the change in virulence. Outbreaks of virulent calicivirus have been isolated and are very rare. Shelter and rescue catteries are the most commonly affected populations. Several epizootics in veterinary facilities have occurred because of the introduction of a sick shelter cat into the veterinary hospital. Because this calicivirus variant is so pathogenic, the disease usually burns itself out in the affected population over several weeks and general spread to and among household pets in the surrounding community has not been reported. However, in at least one case, veterinary personnel handling cats in an affected population have carried the disease to their own pets at home.

HOW CAN I RECOGNIZE THIS DISEASE?

Virulent systemic calicivirus is a very rare disease that most often affects group-housed cats. Typically, the disease emerges as an apparent epizootic of upper respiratory disease that causes severe respiratory signs but progresses to produce cutaneous and systemic complications with a higher than expected mortality rate among affected cats. The incubation period for VS-FCV is 1 to 5 days. Older cats often have more severe disease than younger cats with this unusual calicivirus variant. Keep in mind that this is a very rare variant of feline calicivirus and that the vast majority of cats with clinical signs of upper respiratory disease will have infection caused by the much more common feline upper respiratory disease agents.

HOW IS VIRULENT SYSTEMIC CALICIVIRUS SPREAD AMONG CATS?

Like other caliciviruses, hemorrhagic calicivirus is present in the secretions and excretions of affected cats. Once the virulent mutant appears, spread may occur by direct contact among cats, transfer by hospital personnel handling cats, and via fomites. If an outbreak of VS-FCV is suspected, strict quarantine and isolation of affected cats, and scrupulous cleaning procedures must be initiated to contain the infection and avoid spread of the disease. Hospital personnel should wear protective clothing (gowns, caps, shoe covers) and disposable gloves when handling affected cats. Food bowls, medical equipment, and supplies used in the isolation area should remain there and not be moved in and out of the isolation area. Personnel should wash exposed body parts well and change their clothing and footwear prior to returning home to avoid transmission of the disease to their own household cats. Ideally, the hospital should avoid admitting new feline patients until the disease outbreak is under control.

WHAT SHOULD I DO IF I SUSPECT THAT I HAVE A PATIENT AFFECTED WITH VIRULENT SYSTEMIC CALICIVIRUS?

If you suspect that you have a patient with virulent systemic calicivirus, you should immediately institute the isolation and sanitation procedures described previously. Contact Dr. Janet Foley at the School of Veterinary Medicine, University of California at Davis. Dr. Foley is conducting an ongoing investigation of this disease and may be contacted at: jefoley@ucdavis.edu or (530) 754-7355 for additional information and for recommendations regarding sample submission for testing to definitively diagnose this disease. No new cats should be introduced into the environment unless testing does not identify the presence of hemorrhagic calicivirus or until the disease has run its course in the affected population. Recovered cats may shed infectious virus for several weeks to months post infection so they should not be commingled with susceptible cats during this time.

HOW CAN I PREVENT THIS DISEASE FROM BEING INTRODUCED INTO MY VETERINARY HOSPITAL?

Virtually all nosocomial cases of this disease occurring in veterinary hospitals have occurred because of the introduction of a sick shelter or rescue cat into the hospital environment. The best method to prevent the introduction of this disease is to avoid hospitalizing sick cats from these types of shelter and rescue facilities. If such cats must be admitted into your hospital, they should be kept in strict isolation under barrier conditions as described above to prevent spread to other cats in the hospital population.

DOES VS-FCV OCCUR IN WELL-VACCINATED CATS?

The traditional upper respiratory calicivirus vaccines (containing calicivirus strain F9 or others) do not protect cats against the virulent systemic calicivirus variant. One killed, adjuvanted VS-FCV vaccine is now available. Several other biologics manufacturers are developing feline vaccines that will include the virulent systemic calicivirus antigen and these products should be available later this year.

When virulent systemic calicivirus vaccines are available, should I change my vaccination protocol for cats to include this antigen? There are several important criteria to consider when making any decision about whether or not to change your current feline vaccination protocol or the products you are using. Risk assessment is an important part of this decision making process.

Is virulent systemic calicivirus a disease that commonly produces significant morbidity and/or mortality among cats, particularly among household pets? The answer to this question is no. Although the mortality rate is high, the disease is very rare and outbreaks have almost always involved shelter or rescue cats, not household pets.

The second point to consider is whether the risk of exposure to or infection with this disease is greater than the risk of potential harm from a vaccine product containing this antigen. As you are undoubtedly aware, the American Association of Feline Practitioners Vaccination Protocol recommends limiting the number of antigens administered to cats to those that commonly cause significant morbidity and mortality. This document also recommends using the least reactive vaccine products available to reduce the risk of vaccine induced inflammation in cats.

At the present time, the total number of cats reportedly diagnosed with VS-FCV disease in the past 9 years is less than several hundred. The risk of exposure to or infection with hemorrhagic calicivirus is much less than the potential for chronic inflammation with an adjuvanted vaccine. Furthermore, each calicivirus strain involved in the small number of outbreaks over the past decade is antigenically distinct. No single vaccine strain can be assured of offering cross-protection against any given strain that may arise.

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HYPERBARIC OXYGEN THERAPY IN VETERINARY MEDICINE

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Hyperbaric oxygen therapy (HBOT) has gradually expanded from its traditional place in treatment of decompression illness ("the bends") to a variety of clinical applications globally. Basic science studies have demonstrated HBOT effects and mechanisms of action. Clinical studies on practical applications are abundant in the human medical literature. In July 2006 the 1st International Symposium for the Use of Hyperbaric Oxygenation in Neurosciences was held in Fort Lauderdale, Florida, with presentations from researchers and clinicians in the hyperbaric oxygenation field from around the world. The Veterinary Hyperbaric Medicine Society (VHMS) has recently been formed, and is compiling retrospective and prospective case registries. The data obtained will be useful to help guide more formal clinical studies in veterinary HBOT. This discussion will focus on HBOT treatment methods, physiologic effects, therapeutic effects, clinical uses, and safety issues in large and small animal cases. Specific examples of patients treated with HBOT will be presented.

HBOT CHAMBERS AND ANCILLARY HARDWARE

Therapeutic chambers are now available from veterinary medical manufacturers and suppliers. Experienced professionals are available to assist in designing systems, obtaining and installing chambers, training hospital personnel regarding operation and safety issues, and servicing HBOT equipment. Clinical chambers range in size from monoplace (single patient) design to chambers accommodating multiple patients/caregivers, operating suites, and "walk in" equine chambers. Most chambers require an oxygen supply system capable of large gas volumes delivered at a rapid flow rate. Liquid oxygen tanks and a medical grade oxygen pipeline of large diameter satisfy these requirements. A passive discharge pipeline directs the exhaust gases outside the hospital building. Some chambers have ports allowing (specific) intravenous (IV) lines and/or tubing for assisted ventilation to be connected to the patient during an HBOT session. Current oxygen costs to operate a small animal monoplace chamber may range from approximately $8 to $20 per treatment session depending on chamber design, length of session, pressure employed, and oxygen supply system. The large animal (equine) chambers consume $20 to $40 of oxygen per session.

TREATMENT PROTOCOL (THE "DIVE")

The patient is prepared by examination and body temperature determination. HBOT is generally not given when the small animal's patient's body temperature is greater than 103°F. Equine sessions are not initiated if an adult horse has a fever above 102°F, or a young horse above 103°F. Theoretically, excessive hyperthermia may increase oxygen uptake by tissues, and enhance the chance of oxygen toxicity. The vast majority of patients are quiet and relaxed during HBOT. Occasional patients are given sedation. Acepromazine is the usual drug of choice for small animals. Occasionally, benzodiazepines or barbiturates are employed in canines. Detomidine is sometimes used in the initial sessions for the equine patient. Cotton bandages cover IV catheters. Metal collars are removed. A static inhibitor ground line is secured on a leg (in the small animal chamber). The session begins with a gradual pressure increase to the designated treatment pressure over approximately 15 minutes. The desired treatment pressure may range from 1.5 to 3 atmospheres absolute [ATA] in a 100% oxygen environment. The treatment period "at pressure" may range from 45 minutes to 2 hours. Then, a gradual decompression over approximately 15 minutes is made, and the patient is removed from the chamber. Currently, most of our small animal patients are treated at 2.2 ATA for 45 minutes "at pressure." In patients perceived to be at reduced threshold for seizures, we may employ the low range (1.5 ATA) for the "at pressure" treatment period. The patients are rested at room atmospheric pressure for at least 4 hours between HBOT sessions to minimize the chances of central nervous system (CNS) or pulmonary oxygen toxicity. We treat most patients with twice-daily (BID) sessions, and continue HBOT acutely until marked and progressive improvement occurs (for example, the tetraparetic, paraparetic, or monoparetic patient is using the affected limb[s] with improving strength and function over several days, or the wound is well on its way to resolution). We have treated some patients with follow-up sessions after initial discharge from the hospital. Patients may receive as little as one session (for example, after orthopedic surgery when administered to reduce inflammation and swelling) to as many as 40 or more sessions in chronic disease entities.

PHYSIOLOGY OF HBOT

At normal atmospheric pressures (1 ATA) and while breathing room air, insignificant amounts of oxygen are dissolved and delivered to the tissues via the plasma. Mild increases are possible when oxygen is administered via mask, oxygen cage, intranasally, or intubation. The effects of HBOT are based upon the fact that oxygen delivered to the alveoli under increased atmospheric pressure results in large increases in the amount dissolved in plasma. This can increase the plasma arterial oxygen content from 0.32 vol % [mL O_2/dL whole blood] breathing room air at 1 ATA , to 4.44 vol % at 2 ATA breathing 100% oxygen, and up to 6.8 vol % at 3 ATA breathing 100% oxygen. This dramatic increase in dissolved oxygen (for example, breathing 100% oxygen at 3 ATA) allows diffusion and delivery via the plasma up to 4 times further through the tissues than is possible while breathing room air at 1 ATA. This delivery is independent of the hemoglobin system. Tissue PO_2 measurement devices have demonstrated that oxygen tension remains elevated at >10% of normal for up to 3 hours following a 1-hour HBOT session. Thus, cells and mitochondria in areas where nearby capillary blood flow has been compromised by traumatic, ischemic, or inflammatory processes may receive oxygen subsequent to HBOT, which would otherwise be denied by the underlying pathologic disease process. Hyperbaric oxygen at 2 ATA has been shown to reduce cerebral blood flow up to 25% (by effecting vasoconstriction), reduce nitric oxide production, yet concurrently increase (x10) cerebral oxygen content. Intracranial pressure and cerebral edema are reduced following HBOT. Three recent textbooks offer detailed discussions of the physiology of oxygenation, its relation to HBOT, and effects on the CNS, PNS, and pathologic disease states including the wound healing process.

THERAPEUTIC EFFECTS AND CLINICAL USES

The most common case types treated with HBOT at our small animal facility include intervertebral disk disease, pre- and postoperative spinal surgical cases, fibrocartilagenous emboli, pancreatitis, head trauma, snake bite, and wound care. The common case types treated at equine facilities include extensive, devitalized, or poorly healing wounds, osteomyelitis, intestinal ischemia, birth asphyxia, brachial plexus injury, and radial nerve trauma. We will illustrate case examples with associated literature references in the remainder of this discussion.

Complete Global Cerebral Ischemia

A 1992 paper described a controlled study from Japan where 20 dogs with complete global cerebral ischemia of 15 minutes duration were randomized and divided into two groups. One group received 1 hour sessions of HBOT at 3 ATA in 100% oxygen at 3, 24, and 29 hours after recirculation was established. The control group received room air at 1 ATA. Both groups received nursing support. The HBOT-treated group's mean neurologic recovery score was >65/100 after 5 days, with neurologic recovery scores of >95/100 reached in two dogs from the HBOT group (range: 0 = brain dead to 100 = normal). In contrast, in the group not receiving HBOT, the mean neurologic score remained <60/100 throughout the 14-day follow-up, and only 1 of 10 dogs from the non-HBOT group recovered to a score of > 65/100. 7 of the HBOT group survived to the 14-day follow-up, whereas 3 of the non-HBOT group survived to the 14-day period.

Case example: A 1-year-old M/I Shih-Tzu canine fell off a grooming table while the groomer was distracted, and was accidentally hung by the lead around the neck. Cardiopulmonary resuscitation (CPR) was successful. Acute cortical blindness followed. The patient was given IV methylprednisolone immediately following the resuscitation, and referred for hyperbaric therapy the following day. Low-dose oral prednisolone was continued. Twice-daily HBOT (45-minute sessions at 2 ATA) was given for 7 days. After the second session vision began to return as evidenced by obstacle course performance. Two-week follow-up confirmed improving vision based on owner interview and obstacle course examination. Consultation by an ophthalmologist confirmed resolving cortical blindness. In human cases (near hanging, near drowning, neonatal asphyxia, stroke, cardiopulmonary arrest, etc.), SPECT brain blood flow imaging has been used to demonstrate abnormalities in cerebral perfusion and subsequent improvement following immediate and long-term HBOT. HBOT has been employed in cases of birth asphyxia in foals.

Head Trauma

Many studies have shown that HBOT reduces elevations in intracranial pressure resulting from head trauma in animals and in human head trauma patients. Clinical trials have demonstrated improved survival rates and neurologic recovery scores in human head trauma patients. In addition, improved glucose utilization in rat brain tissue has been demonstrated to persist for up to 24 hours following the last HBOT. There is much contemporary focus and research on the role of matrix metalloproteinases (MMPs) in traumatic brain injury and inflammatory CNS and PNS diseases, including multiple sclerosis (MS) in humans. A change in the balance of certain types of these proteases is associated with cellular infiltrates, apoptosis, and gliosis in traumatic, inflammatory, and neoplastic CNS disease. A 2006 rat model study of traumatic brain injury demonstrated that subjects treated with HBOT had reduced expression of certain MMPs, milder neutrophilic inflammatory infiltrates, and decreased secondary cell death when compared to controls.

Case example: A 3-month-old F/I canine Yorkshire Terrier was hit by a recliner chair. The patient presented obtunded and able to posture only when placed sternally. IV mannitol and ICU oxygen unit therapy were given and a neck brace placed overnight by the E/CC clinicians. BID HBOT was begun the following morning (45-minute sessions at 2 ATA) and continued for 5 days. Marked neurologic improvement was obvious as the patient exited the chamber after the first session, and progressed rapidly until discharge.

Fibrocartilagenous Emboli

Some HBOT studies performed on dogs date back several decades. A 1965 study demonstrated that spinal cord pO2 could be raised by HBOT as long as 72 hours after tissue hypoxia was created in a model of spinal cord injury in canines. Canine cases of fibrocartilagenous emboli often show rapid improvement when promptly treated by HBOT. It is especially important for nursing care and physical therapy purposes to get these primarily large breed patients ambulatory as soon as possible.

Case examples: 1) An 8-year-old M/N Labrador mix was acutely monoparetic, then paraparetic. 2) An 8-year-old F/S Boxer was acutely monoparetic. Clinical diagnoses were based on neurologic examinations, CSF analysis and myelograms were done within a few hours of emergency presentation. Both patients received one dose of parenteral corticosteroids, then low-dose short-term oral prednisolone. Both patients were given BID

HBOT (45-minute sessions at 2 ATA). The Labrador received 14 HBOT treatments, the Boxer 10. It is interesting to note in this acute ischemic myelopathy that patients will often improve markedly as they exit the chamber session, then regress, presumably as pO_2 in the affected cord region drops off. Patients who exhibit this pattern normally improve for longer periods after each session, and eventually maintain their neurologic improvement.

Spinal Cord Trauma, Compressive Lesions, Intervertebral Disk Extrusions

In a 1972 canine model of spinal cord compression, spinal cord tissue pO_2 in the normal cord rose when the subjects were breathing 100% oxygen at 1 ATA. After compressive trauma, the cord pO_2 dropped to near zero on room air, and did not rise when the subjects were breathing 100% oxygen at 1 ATA. When HBOT at 2 ATA was given with 100% oxygen, tissue pO_2 rose sharply even during the compressive period. Neurologic recovery of the HBOT-treated group was improved compared to the control group.

Case example: An 11-year-old Bichon M/N. Acute upper motor neuron tetraparesis with severe neck pain. Normal CSF protein and cytology. Spinal stenosis at a C2-3 fusion site [no history of previous surgery or trauma] and a C3-4 disK extrusion were found on myelographic examnination. Initial treatment was with HBOT (2 ATA, 45 minutes), prior to the diagnostics. At this point the patient became strongly ambulatory. Diagnostics were performed, followed immediately by a limited continuous dorsal laminectomy. Low-dose oral prednisolone and HBOT were given post operatively for 6 days. Progressive clinical improvement was rapid. A desirable effect in neurosurgical cases treated with post op HBOT is rapid surgical wound healing, with reduced swelling, inflammation, seroma, and scar formation. HBOT has become standard pre- and post-neurosurgical adjunctive therapy in our practice, for both spinal and brain surgical cases. We have used HBOT in conservative treatment of documented or presumed spinal cord compressive diseases.

Inflammatory CNS Diseases

We have discussed some of the mechanisms of HBOT anti-inflammatory effects above. The reader should note that in the UK, there are 64 centers (spread out to cover the population density) which are dedicated solely to the treatment of MS in human patients. Over 1.7 million sessions have been completed in the last 24 years without serious incident. Patients generally manage their own long-term treatment schedule, and generally find that their symptoms, especially frequency of micturition, are controlled only by regular HBOT sessions. Some schedule their holidays to be near a "Center." The reader is referred to a detailed chapter on rationale for HBOT in inflammatory disease, including MS in a recent HBOT textbook. A 2006 symposium presentation from a Russian HBOT research clinician described the use of combined HBOT and cyclosporine in the treatment of inflammatory CNS disease in humans.

Case example: A 9½-year-old M/N mixed canine presented for persistent fever, sudden loss of coordination and slight personality change. Neurologic exam supported multifocal CNS lesions. CSF cisternal and lumbar puncture protein and cytology were normal. MRI revealed multiple small mixed size hyperintense T2-weighted lesions throughout the thalamus and rostral brainstem. Most remain hyperintense on T2-weighted FLAIR sequencing. Multiple serologies and PCRs, PARR [LSA] were submitted. A 1/164 positive serology for *E. equi* was the only notable laboratory finding. BID treatments of HBOT (45-minute sessions at 2 ATA over 7 days) were initiated along with cyclosporine, prednisolone, imidocarb, and doxycycline. Neurologic signs improved over a 7-day period, with the owner commenting on a marked improvement at home at the 2-week recheck exam. The immunosuppressive therapy is being tapered very slowly. We have not yet treated inflammatory CNS diseases with chronic HBOT therapy.

Osteomyelitis

This disease entity often has devastating consequences in the equine. Lesions present in critical locations such as the fetlock sesamoids usually result in breakdown and subsequent euthanasia even with aggressive antibiotic therapy. The anti-inflammatory and angiogenic effects of HBOT are ideal here. In addition, increased tissue oxygen tension enhances neutrophil-mediated killing of bacteria. Hyperbaric oxygen is also directly bactericidal for certain anaerobes (such as *Clostridium*), and bacteriostatic for some species of *Escherichia* and *Pseudomonas*. Finally, HBOT enhances the static or cidal effects of certain antibiotics such as sulfonamides, trimethoprim, aminoglycosides, vancomycin, and fluoroquinolones.

Case example: HBOT at 2.5 ATA in 1-hour sessions for (25 total sessions) was used along with appropriate antibiotic therapy to treat osteomyelitis in the medial sesamoid of an equine patient who had begun to break down initially while on antibiotic therapy alone. The patient improved and became clinically normal over 8 weeks.

Case example: An equine presenting with acute tetraparesis was found to have C2 vertebral osteomyelitis on radiographic examination. HBOT and antibiotics resulted in neurologic improvement in 48 hours, and discharge from the hospital in sound condition.

Case example: An equine patient diagnosed with a distal limb infarct was treated over a 1-month period with antibiotics and HBOT, 25 1-hour sessions at 2.5 ATA. Clinical signs resolved and the lytic lesion remodeled. Two months post initial presentation repeat signs of an infarct acutely occurred in the same limb. HBOT is a unique adjuvant therapy, not a "magic bullet."

Wound Healing

Collagen deposition and angiogenesis in wound healing are directly related to tissue oxygen tension.

Tissue oxygen monitoring instruments demonstrate that HBOT markedly increases tissue oxygen tension both during and after the hyperbaric session. This results in more rapid fibroblast migration, collagen deposition, and faster capillary growth. Wound healing and contraction is noticeably more rapid in large wounds after HBOT sessions are initiated.

Case examples: Two equine cases with pre- and post-HBOT photographs demonstrate the visible changes in large wounds when HBOT is applied as part of the treatment regimen. HBOT may also be considered in patients with pressure sores.

Case example: This canine sustained large shearing wounds as she was unknowingly dragged by a rope behind a pick-up truck. This patient was depressed, anorexic, hypoalbuminemic, and very painful when referred for HBOT about one week after the accident. Within 36 hours after referral and three HBOT sessions, the patient was bright, alert, and eating voraciously. Wound healing was rapid. Sessions were given over a 2-week period.

Case example: Photographs immediately before and after a treatment session in a post-op nasal exploratory canine case show how HBOT can dramatically reduce swelling after an extensive surgical procedure.

Major Organ Ischemia

HBOT may be employed in cases with major organ ischemia, such as postsurgical correction of colonic torsion in the equine. In the canine a similar situation exists post-gastric dilatation-volvulus (GDV), where the ischemia-reperfusion injury complex often results in similar clinical complications.

Pancreatitis

This inflammatory process is often severe, effusive, and fatal to canine and feline patients. Recent publications describing experimental rat pancreatitis models demonstrate reduced histopathologic severity and improved survival rate in the groups exposed to HBOT when compared with controls. Our clinical experience is that now even cases with severe, effusive pancreatitis can be given a prognosis which includes a good chance for survival when HBOT is employed along with intensive supportive care.

Case example: A 12-year-old female spayed Labrador who ate a "rotted carcass" in a nearby yard. History, clinical signs, physical exam, radiographs, ultrasound exam, fluid analysis, and PLI (pancreatic lipase immunoreactivity) all supported a diagnosis of pancreatitis. Severe pleural effusion was also present. Twice-daily (BID) HBOT for 45 minutes at 2 ATA was given. By hospitalization day 2 the pleural and peritoneal effusions were nearly resolved. A total of nine sessions were given, and rapid clinical improvement resulted in discharge by day 5. Physical exam one week after discharge was normal. Follow-up PLI and ultrasound exam of the chest and abdomen 3 months later were normal.

Other Clinical Applications of HBOT

Other cases treated with HBOT therapy include acute tetraparesis secondary to atlanto-axial (A/A) luxation, acute peripheral nerve injury, and brain lesions pre- and postoperatively. Decubital ulcers, thermal burns, shearing wounds, near drowning, smoke/CO inhalation, and snakebite are a few of the other clinical applications for which we have employed HBOT. Human medical practice is often limited by "approved indication lists" and diagnosis "codes." For example, in the US, there are currently about 14 indications approved by Medicare, and thus typically funded by third party payers. CO toxicity and decompression illness are the only indications commonly creating neurologic signs which are "approved" by Medicare. The UK has 13 "approved" indications, Japan 20, China 53, and Russia 85. In the latter three countries, the "approved" lists contain disease indications which translate as "severe spinal cord disorders," "acute and severe hypoxic brain disorders," "severe spinal cord injury," "Bell's palsy," "multiple sclerosis," "cranial traumas," "viral encephalitis," "illeus," "sepsis," "non-healing wounds," "osteomyelitis," "burns," and "mountain sickness."

Safety Issues

HBOT should not be administered to patients with pneumothorax, certain older type pacemakers, within 48 hours of doxorubricin, or in a patient currently receiving cis-platinum or bleomycin. Acetazolamide or other carbonic anhydrase inhibitors should be tapered prior to HBOT, as they inhibit oxygen-induced vasoconstriction and increase blood flow to the brain, increasing the chance of oxygen toxicity. Transdermal patches should be temporarily removed. Conservative dosages of narcotic analgesics should be employed prior to HBOT, as increased CO_2 tension secondary to respiratory depression can cause cerebral vasodilatation and predispose to oxygen induced seizures. Insulin dosages should be tapered prior to HBOT therapy. Patients with hyperthyroidism also may have an increased chance for oxygen induced seizures. Vestibular signs may be aggravated due to barostimulation of the ear structures. This said, we have witnessed one mild motor seizure [the patient was an idiopathic epileptic canine] in over five thousand sessions at our hospital. The seizure ended as gradual decompression was initiated. The previously cited textbooks are a good source of detailed information on potential contraindications and specific interactions of HBOT with other therapeutic measures.

The chamber contains 100% oxygen under pressure. Measures should be taken to reduce the chance of fire. The chamber should be grounded. A static grounding limb strap should be considered in small animals. Cotton towels and bandages generate less static than polyester fibers. No flammable materials or electronic devices should be placed in the chamber. No metal collars or skin staples should be used. No alcohol, Vaseline, or flammable based dressings should be used. An emergency master oxygen shut off valve should be installed and known by all personnel. A CO_2 fire extinguisher should be close and functional. A textbook on hyperbaric safety is recommended.

CONCLUSION

Over the past three years it has been very rewarding for the doctors and staff to observe the clinical improvement of many cases treated by HBOT at our hospital. The addition of this treatment modality has resulted in an obvious enhancement of our ability to successfully treat many critically ill patients.

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UNCLE MIKEY'S MAXIMS

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The knowledge explosion has done much to advance the science of veterinary medicine. This article will attempt to fill in the large gap in our modern learnings known as the Art of Veterinary Medicine. After 30 plus years of practice, I would like to share some of the painful lessons of the past and present, otherwise known as "Uncle Mikey's Maxims."

1. Treat for the Treatable

This very important statement forms the basis of the optimistic approach to the sick patient. Many clinicians will periodically find themselves confronted with a very distressed or moribund patient during the "off-hours" when important diagnostic facilities and personnel are unavailable. The patient is dying, you don't know the diagnosis, yet something must be done to stabilize the animal until certain definitive answers are known. Another scenario occurs when the workup must be limited for any number of reasons. The answer — Treat for the Treatable. This is clearly illustrated in the situation where a puppy is examined for an acute onset of dyspnea. The history rules out chest trauma but the physical examination findings include an oral commissure ulceration and moist rales heard especially over the dorsal caudal lung lobes. Without using any diagnostic tests, the clinician begins immediate treatment for neurogenic pulmonary edema resulting from an electric cord bite and saves the puppy's life. This is only one of many examples where it is important to: ATreat for the Treatable Before the Treatable Becomes Non-Treatable.

2. Assumptions Lead to Trouble; Therefore Don't Assume

Perhaps we can extract this lesson from many that we have already learned in everyday life. The main reason for being aware of this common judgment error with our patients is that assumptions can sometimes lead to misdiagnosis and perhaps even the animal's demise. Why assume that a sick, polydipsic, polyuric, middle-aged female dog does not have a pyometra just because the recently recorded signalment of the new patient record denotes previous neutering? Isn't it best to verify this fact verbally with the owner in order to turn an assumption into a certainty or obtain an abdominal radiograph anyway?

3. Always Interpret Clinical Information Within the Context of the Patient's Presentation

Today's veterinarian has access to various forms of advanced medical technology, and in the majority of instances, our patients benefit from the data that is generated. Sometimes, however, clinicians become overly dependent on the laboratory tests and diagnostic instrumentation and come to accept the results at face value without interpreting the information within the context of the patient's presentation. This can result not only in misdiagnosis and in mistreatment of the patient, but it can also lead to added expense and emotional distress for the client as well. This situation can result from sample collection errors, laboratory or instrument errors, or the clinician's unfamiliarity with certain clinical disorders.

4. Avoid Tunnel Vision

This all too frequent human mistake might very well qualify for being the main pitfall of the diagnostician. This is a trap that constantly awaits each of us, and its avoidance requires the utmost of vigilance and discipline. It is so easy to focus our minds on an obvious problem while simultaneously losing sight on the rest of the animal. Take, for example, the middle-aged poodle that is examined for rapid onset cataracts and the clinician who either forgets to inquire about the presence of polydipsia and polyuria or fails to weigh the significance of these important historical facts that might contribute to the diagnosis of diabetes mellitus.

5. Treat Your Patient, Not Just It's Disease

These words of caution are closely related to the tunnel vision problem. The emphasis here, however, is therapeutics, not diagnostics. All medications should be adjusted according to each patient's individual needs and the clinical setting in which they are required. It would be unwise to "treat an abscess" with aminoglycoside antibiotic injections if the animal who "owns" the abscess has chronic renal insufficiency and a serum creatinine level of 6.0 mg/dL.

6. Avoid Overmedicating

This error in medical management usually occurs as a result of the clinician's good intentions to do something helpful. The several problems that result from this practice include toxic drug reactions, excess expense, and sometimes interference with the correct interpretation of laboratory test results and the patient's progress.

It is only after many years of practice, studying, and objective thinking would one hopefully learn when not to use certain medications that he might have used with reflex reaction in the past.

7. Be Honest With Yourself

We have all been anointed with these words of wisdom before. In medicine, there is a special place for this advice in our day-to-day practice situations because our patients' lives depend on our objectivity. Perhaps the best judge and jury of them all is the necropsy.

8. Don't Postpone Today's Urgencies Until Tomorrow

This advice is easily accepted when you think that the main consequence might be a "no tomorrow" for the patient. Diagnostic and therapeutic delays might occur because we are fatigued at the end of a busy day, the patient presents during the off-hours emergency period, or the patient's arrival conflicts with other commitments. Although we might not consciously mean to be neglectful, our subconscious desires might deter us from our professional obligations. Why should a dyspneic animal with severe pleural effusion be forced to agonize overnight until its diagnosis becomes a convenience for his doctor on the following day? Let us never forget that: "Our Patients Can Die Waiting."

9. Think That Common Things Occur Commonly

Remembering this will help you to Treat for the Treatable, especially when certain logistics or restraints impede an expedient diagnosis. This is illustrated in the middle-aged dog that presents during a 3-day holiday weekend (a time when most labs are closed) with a peracute onset of weakness, anemia, icterus, hemoglobinuria, and hemoglobinemia. Here it is important to recognize that these signs are compatible with an acute hemolytic event, and that autoimmune hemolytic anemia is the most common disease in this type of clinical setting. This line of reasoning allows for the immediate treatment of the treatable until proven otherwise.

10. Look Closely At Your Patient; It Will Usually Tell You What's Wrong

The essence of the seasoned diagnostician is having the ability to (1) first recognize that the animal is sick, (2) then be able to localize the exact source of the problem, and (3) plan an initial judicious therapeutic strategy while the diagnostic test results are pending. Obviously one cannot proceed to steps 2 and 3 unless step 1 is realized. This is illustrated in the case of the anorectic and depressed cat that is sick because of pyothorax. This patient cannot be appropriately helped until the clinician first recognizes that the cat has an abnormal respiratory pattern.

This is also illustrated in the dog that postures with an arched back from spinal radicular pain, and the examining clinician misinterprets the signs as abdominal in origin or perhaps even fails to recognize the abnormal posture.

11. Never Let Your Patient Die Without the Benefit of the Silver Bullet – (Steroids)

Most of us tend to find this token bit of philosophy humorous or perhaps potentially dangerous. Although there are many diseases that can worsen as a result of repeated doses of glucocorticoid drugs, there are few (if any) that will progress to the patient's demise from one or two doses of this medication. This is not to imply that the indiscriminate use of glucocorticoid drugs is recommended; it is rather a reminder that animals can die of certain disorders such as nonseptic meningitis, autoimmune thrombocytopenia, IMHA, and acute adrenocortical insufficiency if they do not receive glucocorticoid treatment. Certain empirical therapeutic judgments have their places in medicine, especially when we are practicing under various economic, emotional, and diagnostic constraints.

12. When You Hear Hoofbeats, Look for Horses, but Don't Forget About the Zebras

We can effectively practice medicine by remembering that "Common Diseases Occur Commonly." However there are those occasional situations when that extra amount of knowledge or index of clinical suspicion will facilitate the diagnosis of a not-so-common disease and consequently lead to the patient's cure.

Take, for instance, the dog from Portugal that presents with moderate anemia, fluctuating fevers, hyperglobulinemia and splenomegaly. How many of you can suspect that the Azebra@ in this scenario is *Leishmaniasis*?

13. Never Sell the Basics Short

There is no substitute for the thorough history and physical examination. When the clinical hypothesis cannot be substantiated, go back to Asquare one@ beginning with the basics. As Sir William Osler taught: Trying to practice medicine without a strong foundation is like navigating a ship without a compass in uncharted waters.

14. If You Don't Think It, You Won't Find It

This is easily illustrated in the mature vomiting cat with acute pancreatitis. All too often the clinician will think of many other etiologies, but if he or she doesn't consider acute pancreatitis in the differential diagnosis, the condition will easily be missed.

15. Never Let a Biological Specimen Go to Waste

How many times have we admitted a sick patient only to find 8 to 24 hours later (when the lab results become available) that the animal is a ketoacidotic diabetic? Imagine how beneficial it would have been if we would have tested that patient's urine which was available on the cage floor soon after admission. The same applies to other biological specimens such as feces, sputum, etc.

16. Disaster Lurks Whenever a Patient's Problem is "Routine"

The incident that taught me this painful lesson involved a 2-year-old poodle that went into fulminating anaphylaxis immediately following its yearly vaccination—this patient died. Same for my own kitten that died during a "routine" spay under a surgeon's supervision at the Teaching Hospital. How about the endoscope that perforated a cat's stomach during "routine" gastroscopy under the purview of an experienced endoscopist or the cat that arrests during a bronchial lavage? The saga continues...........

17. If It's Not Getting Worse, Give it a Chance to Get Better

Although this is the "quick serve" period in our society, there are many medical disorders that simply will not commit themselves to our quick-fix mentality. Take, for instance, the patient with hemorrhagic pancreatitis who might very well require up to 4 to 5 weeks of a rather "stormy" convalescence. This insight is essential before calling certain disorders "nontreatable."

18. Don't Stray Too Far from the Patient – The Diagnosis Will Eventually Appear

A lot of different conditions can fall into this situation. Take, for instance, the dog with waxing/ waning episodes of restlessness, hyperventilation, and peripheral vasodilatation that might Asome day@ be explained when its pheochromocytoma is diagnosed. Remaining close to the patient and the pet owner will oftentimes give you that important opportunity to go back to square one and perhaps eventually realize the true diagnosis.

16. Don't Give Your Patient a Disease It Doesn't Deserve to Have

Think about it. It is you and the patient with you having the "power" to apply any label to the signs that you detect. Now stop and ask yourself if you are satisfied with the accuracy of your interpretation and the logic of your mental processing. Quoting Dr. Peter Mere Latham: "*Truth in all of its kinds is most difficult to win, and truth in medicine is the most difficult of all.@*

17. Don't Let Technology Make You Decerebrate

With the availability of advanced medical technology, transtelephonics, and e-mail, how easy it is for clinicians to let go of their basic skills and leave the diagnosing and prescribing to those who haven't even looked at the patient. To keep your skills sharp you must use them. Only then will your patient benefit the most.

21. The Necropsy Is the Clinician's Trial By Jury

The necropsy is oftentimes the pinnacle in the search for truths in medicine for it usually holds the definitive answers for the patient's maladies. Although it might yield the pain of a misdiagnosis, let it be the source of a lesson well learned and one that best not be repeated.

22. The Wisdom of Experience Should Never Be Ignored

Let the fear of aging be offset by the confidence gained from knowing. It is the result of an enormous data processing punctuated by the corrected mistakes of the past. Let the wisdom be complemented with evidence-based medicine to maximize the benefit to out patients.

23. The Diagnostician Should Always Ask Him/Herself These Two Questions: Where Am I With This Patient and Where Am I Going?

These two questions will function as a system of checks and balances during the management of any given patient and hopefully avoid the pitfalls of blind pursuit in search of a diagnosis.

24. If the Patient Isn't Going Where You Expect It to Be Going, Then Go Back to Square One

So often the outcome of a misdiagnosis could have been avoided with a heightened awareness by the clinician in charge. Seek not the false comfort brought about with tunnel vision by allowing each new day to call for a complete reassessment of the clinical findings at hand.

25. In Order to Successfully Treat a Cat. You Must Think Like a Cat

The cat is such a unique creature who takes great offense when we mistakenly handle them as "small dogs". You must respect their independence while simultaneously provide them with the utmost of tender loving care. Always try to deal with them on their terms! Failing to remember this will be an experience not to be forgotten.

26. Avoid the Pitfalls of the Red Herring

Lab errors will cost you and the owner time and expense if you pursue nonsensical results. When in doubt repeat the test or speak with the lab technician.

27. If They Can't Afford a Caddy Then Offer Them a Chevy

All too frequently the most expensive tests and treatments are not the sole means of an optimistic outcome.

28. Know Thy Patient

It is essential that you remember all historical and clinical details about your patient so that no vital information is forgotten—this includes a physical examination done with the patient out of the cage on each day of hospitalization.

29. Nobody Wants to Pay for Big Bill and a Dead Animal

This especially applies to the emergency doctor who frequently has situations and issues that need immediate attention. Bottom line is to get compensated as soon as possible or be prepared to suck-up the loss.

30. What Matters is Not So Much What You Say to a Concerned Client, But How They Perceive What You Said

The absence of eye contact, the pressures of on-going catastrophes, and the mounting build-up of fatigue all contribute to the misunderstandings that might end up before an ethics review board. Never forget that your pet owners demand compassion and respect— always.

31. Diagnostic Cloudiness Will Soon be Replaced by Clear Skies – Be Patient

The difficult-to-diagnose patient can lead to frustrations and sometimes wrong decisions. If it is not a life-threatening problem, give the disorder time to unveil.

UNCLE MIKEY'S MAXIMS

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3. Always interpret clinical information within the context of the patient's presentation.
4. Avoid tunnel vision.
5. Treat your patient, not just its disease.
6. Avoid overmedicating.
7. Be honest with yourself.
8. Don't postpone today's urgencies until tomorrow.
9. Think that common things occur commonly.
10. Look closely at your patient; it will usually tell you what's wrong.
11. Never let your patient die without benefit of the silver bullet.
12. When you hear hoofbeats, look for horses but don't forget about the zebras.
13. Never sell the basics short — They are still the best buy in town.
14. If you don't think about it, you won't find it.
15. Never let a biological specimen go to waste.
16. Disaster lurks wherever a patient's problem is "routine."
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29. Diagnostic cloudiness will soon be replaced by clear skies.

UPDATES IN MANAGEMENT OF CHRONIC KIDNEY DISEASE

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Chronic renal failure (CRF) is primary renal failure that has persisted for months to years. The newer term applied to CRF is *chronic kidney disease* (CKD), recognizing that the disease has a spectrum of severity from asymptomatic kidney disease to end stage uremia. The percentage of dogs and cats with CKD increases with increasing age. In two studies of dogs and cats admitted to teaching hospitals, approximately 10% of dogs and 30% of cats over 15 years of age were diagnosed with CKD. Although CKD tends to be stable over the short term, CKD tends to progress to end-stage renal failure over months to years in many animals. In the proposed IRIS staging system, CKD is classified into stages based on stable serum creatinine concentration and into substages based on level of proteinuria and hypertension (Tables 1, 2, and 3).

Clinical signs of CKD include anorexia, vomiting, dehydration, weight loss, lethargy, polyuria/polydipsia (PU/PD), oral ulceration, ptyalism, anemia, social apathy (cats), and constipation. Cats with CKD have a history of PU/PD less commonly than dogs, and many cats with mild to moderate CKD are asymptomatic. Diagnosis of CKD per se requires documentation of azotemia with inappropriate urine concentrating ability (USG < 1.030 in dogs or USG < 1.035 in cats) along with evidence of chronicity. Abdominal palpation of small kidneys (or decreased renal size based on radiography), nonregenerative anemia, renal osteodystrophy, or serial documentation of prior azotemia are supportive evidence of CKD rather than acute renal failure. However, in one study, the incidence of non-regenerative anemia was similar in dogs with CKD versus acute renal failure (ARF). Anemia in ARF may be attributed to acute blood loss from uremic gastrointestinal ulceration. Indications of ARF include cylindruria (casts), known exposure to a nephrotoxin (anti-freeze, gentamicin) or an episode of severe hypotension, recent lab data demonstrating normal renal function, and a rapid decline of renal function over 24–l48 hours without prerenal or postrenal factors. ARF may occur in animals with CKD (acute on chronic) because animals with pre-existing renal disease are most susceptible to ischemia and toxins. With ARF on CKD, recovery of renal function will only be less than or equal to original level of renal function. The following do **not** help to differentiate between CKD and ARF: BUN, creatinine, phosphorus, calcium, TCO_2, urine specific gravity.

Some cats loose urine-concentrating ability and become azotemic at about the same level of renal dysfunction. However, it is not uncommon for cats to

Table 1. IRIS CKD Staging by Serum Creatinine Concentration

Stage	Creatinine (mg/dL)	Comments
I	<1.4 dogs <1.6 cats	Non-azotemic Confirmed renal disease present
II	1.4-2.0 dogs 1.6-2.8 cats	Mild renal azotemia (lower end of the range overlaps within reference) Clinical signs usually mild or absent
III	2.1-5.0 dogs 2.9-5.0 cats	Moderate renal azotemia Many extrarenal clinical signs may be present
IV	>5.0 dogs and cats	Severe renal azotemia Many extrarenal clinical signs are usually present

Table 2. IRIS Substaging by UP/C Ratio

UP/C value	Interpretation
<0.2 dogs and cats	Non-proteinuric (NP)
0.2–0.4 cats 0.2–0.5 dogs	Borderline proteinuric (BP)
>0.4 cats >0.5 dogs	Proteinuric (P)

Table 3. IRIS Substaging by Blood Pressure

Risk*	Systolic (mm Hg)	Diastolic (mm Hg)
Minimal	<150	<95
Low	150–159	95–99
Moderate	160–179	100–119
High	≥180	≥120

**Risk = likelihood that high pressure will further damage the kidney and other end organs.*

retain their ability to concentrate urine slightly above 1.035 with early CKD. Concurrent drug therapy or diseases that impair urine-concentrating ability (eg, diuretics, hyperthyroidism) make localization of azotemia to renal versus prerenal based on urine specific gravity more difficult.

The prognosis of CKD must be assessed short-term and long-term. Short-term prognosis depends on the level of renal function present once all prerenal and/or postrenal factors are removed. It is also affected by concurrent diseases and complications of CKD (eg, hypertension, anemia). Animals' tolerance of different levels of azotemia is highly variable. Animals with CKD adapt gradually and tolerate more severe azotemia without uremic signs compared to animals with acute azotemia. Other factors, such as anemia, affect tolerance of azotemia. Most CKD dogs and cats tolerate BUN concentrations <75 mg/dL with few uremic signs. However, the long-term prognosis is generally guarded to poor because of progression to end-stage kidneys. Removal of underlying cause of the renal failure may allow stabilization or slight improvement in glomerular filtration rate (GFR). Once a critical threshold of renal mass is lost, renal failure *tends* to become self-perpetuating.

DIETARY TREATMENT OF CHRONIC RENAL FAILURE

Dietary treatment of early CKD in dogs and cats continues to be controversial with respect to what dietary components are important to prevent progressive renal functional loss and uremia. Recent studies show that renal diets result in lower mortality from uremic crises and uremic death compare to maintenance diets in both dogs and cats with stage II-III CKD. There is no proof that dietary protein restriction per se slows progression of CKD in dogs and cats so it is not known exactly *why* renal diets are beneficial. Dietary phosphorus restriction slows progression of CKD in dogs, but this has not been proven in cats. Studies are also currently evaluating the affect of dietary acid–base balance and dietary lipids on progression of CKD in dogs and cats. Highly acidified diets designed for prevention of struvite urolithiasis are poor choices for cats with CKD. These diets assume that the kidneys will excrete the excess dietary acid load in the urine, thereby acidifying the urine. However, if the kidneys can not effectively excrete the excess acid load due to CKD, the net effect is acidification of the cat rather than the urine. Diets high in ω-3 fatty acids (menhaden fish oil) are beneficial in treatment of some models of CKD and immune-mediated GN compared with diets supplemented with ω-6 fatty acids.

Despite the academic controversy of what type of diets to feed cats (and dogs) in early CKD, most veterinarians currently recommend diets that are restricted in protein and phosphorus content, replete in potassium content, and that contain adequate buffering capacity (an alkalinizing diet). Having a low ratio of ω-6 to ω-3 fatty acids (≤ 5:1) is also desirable. Regardless of the type of diet fed, it is more important that dogs and cats with mild to moderate CKD maintain adequate caloric intake to avoid protein-calorie malnutrition. Monitoring for evidence of protein-calorie malnutrition should include monitoring for weight loss, hypoalbuminemia, poor hair coat quality, muscle wasting and declining body condition scores. Dietary treatment of moderate to severe CKD is **not** controversial. Dietary protein and phosphorus restriction are required to avoid uremic complications in animals with more advanced CKD (serum creatinine > 5 mg/dL).

Delivery of the renal diet is also very important because low protein diets tend to be less palatable. This is compounded by the nausea and anorexia typical of moderate to severe CKD. Gradual transition to the renal diet over 2 to 4 weeks resulted in excellent acceptance of the diet in one clinical trial. Diet consumption may be encouraged by heating the food to room temperature, adding small amounts of water, tuna water or clam juice (cats), or adding garlic powder (dogs). Alternatively, a few dogs will eat dry renal diets better if the diet is frozen. If the dog or cat will not consume adequate calories, long-term feedings tubes (percutaneous endoscopic gastrostomy [PEG] tubes) can markedly improve nutritional status and facilitate administration of fluids and medications. Although most clients are hesitant initially, client and patient acceptance of long-term feeding tubes are usually excellent.

MEDICATIONS: BEYOND DIETARY THERAPY

In addition to changing the cat's diet, a number of medical therapies may improve the quality of life for cats with CKD. Cats with CKD have increased a serum gastrin concentration, which contributes to the pathogenesis of uremic gastritis. Unfortunately, many cats with uremic gastritis only show partial to complete anorexia as the clinical signs of this problem rather than vomiting. Therefore, H_2 receptor antagonists are underutilized by many veterinarians in treatment of CKD. **Famotidine** (0.5–1 mg/kg PO q 24 h for dogs or 5 mg per cat PO q 48 h) is recommend for treatment of uremic gastritis secondary to CKD once the serum creatinine is above 2.5 to 3 mg/dL. For more severe uremic gastritis, omeprazole or ondansetron may be required to control vomiting.

Intestinal phosphate binding agents should be instituted when dietary phosphorus restriction fails to maintain serum phosphorus concentrations within the normal range. Aluminum hydroxide (30–100 mg/kg/day PO with meals) is the most common intestinal phosphate binder recommended. Calcium carbonate (90–150 mg/kg/day PO with meals) or calcium acetate (60–90 mg/kg/day PO with meals) may be used as alternatives to aluminum-containing intestinal phosphate binders; however, hypercalcemia may occur when combined with calcitriol therapy. Aluminum- and calcium-containing phosphate binders may be used in combination to reduce the dose of each and minimize the risk of hypercalcemia.

A recent placebo controlled, double-masked study confirmed that **calcitriol** to treat renal secondary hyperparathyroidism is beneficial. There was a 68% reduction in mortality in the calcitriol treated group compared with placebo. Because elevated parathyroid hormone (PTH) concentration may act as a uremic toxin and may contribute to progression of CKD, calcitriol (3.5–6 **ng**/kg/day PO) should be initiated once the serum creatinine concentration is above 5 mg/dL and if elevated PTH concentrations are documented. However, this should only be done after dietary phosphorus restriction and addition of phosphate binders. Also, this therapy requires regular monitoring of ionized calcium and PTH levels and should **not** be used unless the owner will comply with follow-up recommendations. If hypercalcemia occurs, the dose of calcitriol should be decreased changed to pulse therapy. Monitoring of ionized calcium and PTH concentrations is the preferred method of monitoring calcitriol therapy. Calcitriol dose maybe gradually increased up to 6 ng/kg as needed to reduce PTH levels or until ionized hypercalcemia occurs, whichever occurs first. Calcitriol in compounded dosing is available from veterinary compounding pharmacies

Anemia of CKD is mainly due to a relative deficiency of erythropoietin. Iron deficiency may contribute to anemia due to uremic GI ulceration causing chronic blood loss. Protein malnutrition may also contribute to anemia if protein intake too severely restricted. Blood transfusions may be used to temporarily correct the anemia of CKD but are not practical long-term. Recombinant human erythropoietin (**r-HuEPO**) is commercially available as Epogen or Procrit. Treatment of cats with anemia secondary to CKD using r-HuEPO results in rapid correction of the anemia in a dose dependent fashion. The loading dose is 75 U/kg (cats) or 100 U/kg (dogs) SQ three times per week until Hct is in the low normal range. Once the target range is achieved, the maintenance dose is 50 to 75 U/kg SQ 1 to 2 times per week as needed to maintain hematocrit in the low normal range.

Recombinant human erythropoietin is a human protein attached to human albumin. Therefore, r-HuEPO is potentially antigenic to dogs and cats resulting in development of anti-EPO antibodies in approximately 30% of animals treated with r-HuEPO. These anti-EPO antibodies cross react with the endogenous EPO causing a severe nonregenerative anemia. Cats that develop anti-EPO antibodies become transfusion dependent until antibody levels decrease 2 to 4 months after discontinuation of the drug. Because of this potentially serious side effect, I currently reserve treatment with r-HuEPO *until* the cat has sustained anemia with hematocrits below 15 to 18%. Iron deficiency is relatively a common sequela of r-HuEPO therapy resulting in poor responsiveness to r-HuEPO therapy. Therefore, I recommend supplementing all dogs treated with r-HuEPO using oral ferrous sulfate at a dose of 100–300 mg/dog/day and cats with a dose of 50–100 mg/cat/day (10 mg/kg/day).

Canine r-EPO and feline r-EPO was tested in a multi-center clinical trial. The main advantage of species-specific EPO is that it avoids antibody production common with r-HuEPO. Species-specific erythropoietin will change our approach to dogs and cats with mild anemia secondary to renal disease if they become commercially available.

MONITORING THERAPY

Monitoring plans for CKD patients depends on the diet and treatment protocol. At a minimum, CKD patients should be re-evaluated of monthly, then every 3 to 6 months as needed. More frequent evaluations are necessary to monitor therapy such as antihypertensive agents, phosphate binders, calcitriol, erythropoietin or potassium supplements. Re-evaluation should include history, physical exam, body weight, body condition score, packed cell volume (PCV) (or complete blood count [CBC]), serum biochemistry panel, urinalysis, periodic urine cultures, and blood pressure determination. Appropriate medical follow-up is high-quality medicine and generates income for your practice. It may be useful to plot serum creatinine and body weight on a chart in the medical record to monitor tends over time.

Animals with CKD commonly become dehydrated because of illness or lack of access to water and decompensate their CKD because of superimposition of prerenal azotemia on top of renal azotemia resulting in a uremic crisis. This does not equate to terminal renal failure. Appropriate medical management may allow recompensation and continuation of a good quality life depending on remaining renal function. The basis of treatment of uremic crisis is removal of prerenal and/or postrenal components and treatment of concurrent diseases. Estimated fluid deficit should be replaced intrave nously (IV) over 2 to 6 hours with a replacement fluid (high sodium fluid such as LRS, saline, or Normosol-R based on serum electrolytes). The maintenance fluid rate will usually be greater than normal (2 to 3 times maintenance) because of polyuria. Fluid rate should be adjusted to meet the patients need to prevent dehydration, not given arbitrarily at __ x maintenance. Monitoring parameters useful for renal failure patients receiving fluid therapy include body weight (1–2x/day), thoracic auscultation to monitor for pulmonary edema (q 2–4 hours), PCV/TPP (1–2x/day), serum chemistry panel (q 1–3 days as needed), urine output (rarely needed), skin turgor and central venous pressure (CVP). H_2 receptor antagonists are useful to decrease gastric acid secretion (hypergastrinemia). Cimetidine dose is usually used at 10 mg/kg IV; then 5 mg/kg IV q 12 h (inhibits P450 enzyme system). During initial uremic crisis with vomiting and anorexia do not feed orally. Once the vomiting has stopped and/or azotemia reduced, food is reintroduced as frequent small meals. Nutritional support using nasoesophageal tubes should be used if anorexia last more than 2 to 3 days. Fluids do not need to be tapered in animals with CKD. Consider daily or every other day subcutaneous (SQ) fluid administration if dog or cat is unable to maintain hydration and/or prevent repeated uremic crisis. An alternate is use of PEG tube feeding to provide nutritional and fluid support (see above).

SUBCUTANEOUS FLUID THERAPY

In dogs and cats with more advanced CKD, administration of subcutaneous fluids such as lactated Ringers solution (LRS) or Normosol-R daily or every other day may be beneficial. However, this should not be implemented too early because of the sodium content of isotonic fluids. Subcutaneous fluid therapy does NOT increase the GFR above what the kidneys are capable of provided they are normally perfused. It does help keep the animal well hydrated and allow some increased elimination of blood urea nitrogen (BUN) through increased tubular flow rates. Urea is normally reabsorbed from the tubules to help establish and maintain the medullary concentration gradient. With increased tubular flow rates, less urea is reabsorbed (more excreted in the urine), lowering the BUN. Keeping the animal well hydrated prevents additional increases of the BUN and creatinine due to prerenal causes in addition to the renal azotemia. I caution owners that if the CKD animal is completely anorexic, normal electrolyte balance will not be maintained with SQ fluids alone. In CKD cats prone to hypokalemia, add up to 20 mEq of KCl per liter.

Subcutaneous fluids are usually administered via 20-gauge needles. Because some animals and/or owners object to repeated needle injections of subcutaneous fluids, recently developed "needleless" systems connected to an implantable silicone subcutaneous catheter can be used for administration of fluids by the owner at home. Strict aseptic technique must be used in placement and maintenance of these SQ catheters to prevent catheter-associated infections. These catheters may be left in place for several months to a year unless they become infected.

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RECURRENT URINARY TRACT INFECTIONS

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One of the most common referral problems encountered in veterinary urology is recurrent urinary tract infection (UTI) in dogs. There are two major types of UTI recurrence: relapses or reinfection. The implications of relapse versus reinfection are important for diagnosis and management of recurrent UTI. **Relapses** are UTI recurrence of the same species and serologic strain of microorganisms within several weeks of withdrawal of therapy. **Reinfections** are recurrent infections caused by a different pathogen from the previous UTI.

WHAT ARE CAUSES FOR RECURRENT UTI?

Common causes of **relapse** include inappropriate antibiotic use (incorrect dose or duration, poor owner compliance), failure to eliminate predisposing causes (uroliths, neoplasia), deep-seated infections inaccessible to the antibiotic (pyelonephritis, prostatitis), and emergence of drug-resistant pathogens. Common causes of **reinfection** include failure to eliminate predisposing causes for UTI, presence of multiple pathogens in which only sensitive pathogens were eliminated by therapy, iatrogenic infection during follow-up procedures (catheterization), and spontaneous reinfection.

There are normal host defenses that protect the urinary tract from infection. Breakdowns in these defenses result in UTI if bacteria gain access to sterile portions of the tract. Normal voiding washes bacteria out of the urinary tract. Normal canine and feline urine is bactericidal from high osmolality and extremes in pH (<6.0). Urothelium has several intrinsic antibacterial properties. Mechanical factors (urethral high pressure zone, length of urethra, urethral and ureteral peristalsis, and ureterovesical "flap valves") act as mechanical barriers to ascending UTI.

Most UTIs occur from ascending bacterial infection. Anything that interferes with the normal host defenses listed above may contribute to repeated ascending infections. Common contributing factors include incomplete voiding, urine stasis or reflux, disruption of or damage to the urothelium, alterations in immune competence, alterations of urine composition (dilute urine, glucosuria), or iatrogenic causes (perineal urethrostomy, indwelling urinary catheters). Although young adult cats rarely have bacterial UTI unless prior procedures predispose them to acquired UTI, older cats are more commonly affected by UTI because of concurrent diseases that cause dilute urine and or impair immune competence.

WHAT IS THE DIAGNOSTIC APPROACH FOR ANIMALS WITH RECURRENT UTI?

The standard **diagnostic evaluation** for dogs with recurrent UTI should include complete blood count (CBC), serum biochemistry profile, urinalysis, urine culture, abdominal radiographs, and ultrasound. The history should be reviewed for diseases or drugs that could contribute to immunosuppression. Physical examination should include careful examination of the vulva and per-vulvar skin for evidence of recessed or “hooded” vulva that may contribute to reinfection of the urinary tract. Subtle abnormalities of the perivulvar region are easily overlooked during routine physical examination and should be carefully evaluated in dogs with recurrent UTI.

Testing for hyperadrenocorticism should be performed if there is any supportive data. In our hospital, cystoscopy has become a standard part of the diagnostic evaluation for dogs with recurrent UTI if an underlying cause has not been identified during initial workup. Cystoscopy helps rule out anatomic abnormalities, neoplasia or uroliths and permits mucosal biopsy for culture, cytology and histopathology. Furthermore, ureteral catheterization can also be performed to obtaining cultures of the upper urinary tract.

Other Types of Cultures

Cultures of tissue or uroliths are more sensitive than simple urine culture for detecting chronic infection especially in dogs previously treated with antibiotics. In one study, bacteria were isolated from mucosal or urolith cultures in 18.5% of dogs with negative urine cultures. Mucosal samples for culture can be obtained at surgery or during cystoscopy. We have been able to identify Mycoplasma UTI more consistently from cultures of mucosal biopsies obtained during cystoscopy than from urine obtained by cystocentesis.

WHAT IS THE THERAPEUTIC APPROACH FOR ANIMALS WITH RECURRENT UTI?

Treatment of recurrent UTI (after search for an underlying cause) should be based on culture and sensitivity of urine obtained by cystocentesis. A follow-up urine culture should be obtained 7 to 10 days into therapy to prove in vivo efficacy of the drug selected from in vitro susceptibility testing. Provided the initial culture is negative, antibiotic therapy is continued at full doses for a total of 4 to 6 weeks depending on location and type of infection (6–8 weeks for suspected kidney or prostate involvement). Urinalysis and urine culture should be repeated 1 week and 1 month after completion of antibiotic therapy.

Episioplasty is usually effective for resolving re-infections that occur secondary to perivulvar dermatitis. Resolution of relapsing UTI secondary to infected uroliths usually requires removal of the uroliths in order to achieve resolution of the UTI.

Preventative therapy for repeated **reinfection** (>2 per 6 months) should **only** be utilized after an extensive search for any underlying cause. Preventative therapy consists of giving a single dose of an antibiotic immediately before bedtime after the dog has urinated. The rationale is to attempt to assist the normal host defenses against ascending UTI before a new infection can become established. This approach will **not** resolve existing UTI and should only be used after effective treatment using full therapeutic doses. For dogs that have recurrent gram-positive bacteria causing UTI, I usually recommend amoxicillin (20 mg/kg) given PO once daily. For dogs with re-infections with gram negative organisms, I usually use either a first generation cephalosporin or nitrofurantoin (4 mg/kg PO once a day). Nitrofurantoin may rarely cause drug-induced hepatopathy and liver enzymes should be evaluated if any adverse effects are suspected. Preventative therapy will **not** be effective for **relapses** of the same organism due to a nidus within the urinary tract. Likewise pulse antibiotic therapy for 3 to 5 days every few weeks is **not** an effective strategy for management of recurrent UTI. These misuses of antibiotics are likely to induce multiple drug resistance in the organisms causing the UTI and limit the number of effective antibiotic options available for treatment of new or recurrent infections.

An alternative therapy for recurrent UTI is use of a rarely used urinary antiseptic **methenamine mandelate**. Methenamine is converted to formaldehyde in an acidic urine pH. Because bacteria can not acquire resistance to formaldehyde, it may be efficacious in patients with resistant UTI and in patients with re-infections despite night-time preventative doses of antibiotics. The dose is not well established but recommended doses are 10 to 20 mg/kg PO every 8–12 hours. If necessary, urine pH may need to be lowered by use of an acidifying diet and/or urinary acidifiers.

WHICH ORGANISMS CAUSING RECURRENT UTI POSE SPECIAL DIFFICULTY?

Mycoplasma UTI is an uncommon cause of recurrent UTI that may be associated with co-infection with bacteria are slow growing, fastidious organisms. Because of their small size, you are unlikely to see them on urinalysis. *Mycoplasma* spp. lack a rigid cell wall which affects the antibiotics that are effective against them. *Mycoplasma* spp. are normal inhabitants of the lower portion of the urogenital tract. In two large studies, *Mycoplasma* was the eighth most common pathogen causing UTI overall in dogs (2.5%) and it was the ninth most common organism causing persistent or recurrent UTI in dogs.[7,8] Indications to consider mycoplasma UTI include persistent pyuria despite negative urine cultures, abnormally alkaline urine pH, or dogs with persistent or recurrent UTI that have not responded to conventional therapy. Treatment of mycoplasma UTI is usually with fluoroquinolones or doxycycline. I usually recommend 4 to 8 weeks of therapy with urinalyses every 2 to 4 weeks to see if the initial signs of UTI have resolved and for follow-up cultures.

Enterococcus spp are also increasing in frequency as a cause of recurrent UTI, especially in dogs that have been treated with fluoroquinolones. There are several important features of this organism that contribute to frequent recurrence. During laboratory *in vitro* susceptibility testing, Enterococcus often appears to be susceptible to fluoroquinolones, although it is usually resistant to fluoroquinolones in vivo resulting in treatment failure. One textbook also lists that *Enterococcus* is able to overcome folic acid blockade in vivo and may be resistant to potentiated sulfas despite in vitro susceptible test results. Some animals with enterococcal UTI have no symptoms of their UTI for extended periods of time. There is a notable absence of pyuria in these animals with silent enterococcal UTI. In rare patients, enterococcal UTI may remain unresolved despite appropriate antibiotic therapy.

E. coli UTI also warrants some additional comments with respect treatment of recurrent UTI. Because of their ability to acquire antibiotic resistance through plasmid mediated resistance, *E coli* UTIs can become multi-resistant over time. Therefore, appropriate follow-up is especially important with this common uropathogen. Routine follow-up cultures are recommended for any dog or cat with recurrent UTI due to *E. coli*. For multiresistant *E. coli*, antibiotics to consider if testing suggests they are effective include amikacin, ceftiofur, imipenem, or meropenem. Aminoglycosides are excreted in the urine and achieve very high urine concentrations but are also nephrotoxic. Therefore, aminoglycosides should only be used for shorter durations and with appropriate monitoring for nephrotoxicity. Monitoring for nephrotoxicity should include routine urinalysis and monitoring of urine GGT to creatinine ratios. Ceftiofur (3–4 mg/kg SQ every 24 hours) is a safer alternative to aminoglycosides provided the *E. coli* isolated is sensitive in vitro. Imipenem or meropenem are highly effective against many strains of *E. coli* and may be required in animals with renal disease and recurrent gram-negative UTI. However these, antibiotics should be reserved for documented multiresistant infections when other antibiotics have failed and renal disease prohibits the safe use of aminoglycosides.

WHAT ABOUT CATS THAT HAVE RECURRENT UTI?

Cats less than 8 to 10 years of age uncommonly have bacterial UTI as a cause of lower urinary tract signs unless they have had perineal urethrostomy surgery or indwelling urinary catheters. The incidence of lower urinary tract disease in **geriatric cats** is very different than young adult cats. In one study, 46% had UTI (2/3 with concurrent chronic renal failure), 17% had UTI and uroliths, 10% had uroliths, 7% had urethral plugs, 7% were due to trauma, 5% had idiopathic cystitis, and 3% had neoplasia.

CONCLUSIONS

The key to successful management of recurrent UTI is to accurately diagnose the reason(s) for the recurrent nature of the problem in each case. Cystoscopy is an underutilized tool in the diagnosis of recurrent UTI. Appropriate follow-up cultures are often key to successful management of recurrent UTI.

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MINIMALLY INVASIVE MANAGEMENT OF UROLITHS

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Traditionally in veterinary medicine removal of bladder and urethral stones has been by open surgical procedures such as cystotomy and urethrotomy; however, many uroliths can be effectively managed by nonsurgical or minimally invasive techniques including medical dissolution, voiding urohydropropulsion, laser lithotripsy, and laparoscopic-assisted cystotomy. Furthermore, effective treatment of urolithiasis always involves two components: removal of uroliths and prevention of recurrence. Surgical removal is usually effective regardless of the location and type of urolith. Surgical removal is preferred for male cats with uroliths causing recurrent urethral obstruction and for urolithiasis complicated by anatomic defect which could be surgically corrected during urolith removal. Other than these situations, minimally invasive management techniques often can be used to replace open surgical removal.

MEDICAL DISSOLUTION

Medical dissolution is effective for certain locations and types of uroliths. Uroliths that may be medically dissolved include struvite, urates, and cystine. For dissolution to occur, the urolith should be surrounded by under-saturated urine to allow the crystals to go back into solution. Urocystoliths and nephroliths are amenable to dissolution but ureteroliths and urethroliths are not. Urethroliths may be flushed back into the urinary bladder by retrograde urohydropropulsion for medical dissolution or mechanical removal. Medical dissolution is usually effective for struvite uroliths in dogs and cats, and for urate and cystine uroliths in dogs. Calcium oxalate and silica uroliths can not be medically dissolved. Medical dissolution of urocystoliths in male animals is associated with a risk of urethral obstruction once the urocystoliths are small enough to pass into the urethra. Therefore, the clinical signs of urethral obstruction should be thoroughly explained to the owner if medical dissolution is considered. Once uroliths are removed, preventative therapy should be initiated to reduce recurrence.

Medical dissolution of struvite urocystoliths requires a combination of appropriate antimicrobial and calculolytic dietary therapy. Antimicrobial selection should be based on urine culture and antibiotic-susceptibility testing from urine obtained by cystocentesis prior to antimicrobial therapy. Antimicrobial therapy must be given throughout the entire dissolution period because viable bacteria are contained within layers of struvite uroliths. For sterile struvite uroliths which mainly occur in cats, antimicrobial therapy is not necessary, but monitoring for development of urinary tract infection (UTI) is recommended. Two commercial calculolytic diets are available for dissolution of struvite uroliths in dogs: Hill's Prescription diet s/d® and Royal Canin (Waltham®) Canine S/O Lower Urinary Tract Support Diet. Hill's Prescription diet Canine s/d® has been proven to be effective for dissolution of struvite uroliths in dogs.[1] Royal Canin (Waltham®) Canine S/O Lower Urinary Tract Support Diet was effective for dissolution of canine struvite uroliths in an *ex vivo* model. Antimicrobial and dietary therapy should continue approximately 1 month beyond radiographic resolution of struvite urolithiasis (because uroliths too small for radiographic detection may still be present) or until resolution of all uroliths on ultrasonography. The animal should not be in renal failure and should not have evidence of obstruction. Five to 7 days after initiation of antimicrobial therapy, urine should be obtained by cystocentesis for urinalysis and culture. Urinalysis should reveal decrease of the urine pH to <7.0 and the urine culture should be negative for bacterial growth. If the UTI is persistent, antimicrobial therapy should be changed on the basis of urine culture and sensitivity testing. Monitoring of dissolution therapy should consist of abdominal radiographs and urinalyses every 4 weeks. If bacteruria, pyuria or inappropriate alkaline urine pH are present, the urine should be cultured for aerobic bacteria and mycoplasma.

Medical dissolution of canine urate urolithiasis can be attempted using a protein-restricted, alkalinizing diet (Hills Prescription diet Canine u/d®), allopurinol (15 mg/kg PO q12h), and supplemental potassium citrate as needed to maintain a urine pH of approximately 7.0. Medical dissolution of canine cystine urolithiasis can be attempted using a protein-restricted, alkalinizing diet (Prescription diet Canine u/d, Hills), 2-MPG (Thiola®, 15 mg/kg PO q12h), and supplemental potassium citrate as needed to maintain a urine pH of approximately 7.5. Struvite preventative diets are preventative for struvite urolithiasis only, as they may promote the formation of other urolith types (uric acid, calcium oxalate, and cystine). Prevention and treatment of recurrent UTI is critical for prevention of infection-induced struvite uroliths.

VOIDING UROHYDROPROPULSION

Voiding urohydropropulsion is the removal of smaller urocystoliths by inducing voiding while the dog is positioned vertically so that urocystoliths pass during voiding. General anesthesia facilitates complete urethral relaxation, preventing development of high intravesicular pressures that could cause iatrogenic trauma to the bladder wall. If the bladder is not distended with urine, it is distended with sterile saline via cystoscopy or urethral catheterization. The dog is positioned so that the spine is roughly 25 degrees caudal to a line perpendicular to the effects of gravity, such that a line drawn through the urethra into the bladder is approximately vertical (Figure 1). The bladder is agitated, and the urocystoliths to settle in the trigone by gravity. The bladder is palpated and the intravesicular pressure is gradually increased by manual compression of the bladder to initiate a detrusor contraction. Once voiding begins, the bladder is compressed more firmly to attempt to maintain maximum urine flow to flush out the urocystoliths. The bladder is refilled with sterile saline through the cystoscope or a urinary catheter and the process is repeated until no urocystoliths are passed with the expelled fluid. Then post-procedural radiographs (or cystoscopy) are performed to confirm complete removal of the urocystoliths. Peri-procedural antibiotics are recommended to prevent iatrogenic UTI.

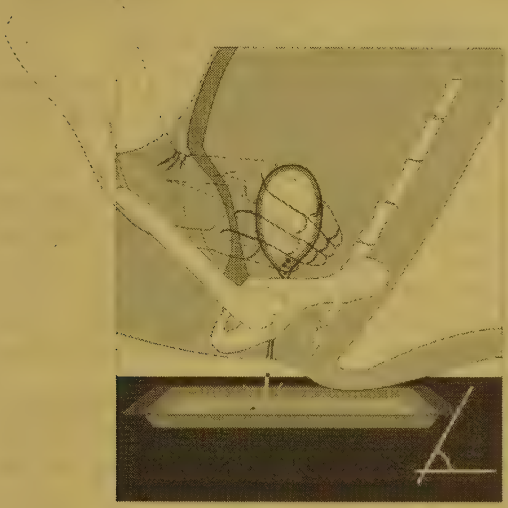

Figure 1. Positioning for voiding urohydropropulsion.

RETROGRADE UROHYDROPROPULSION

Retrograde urohydropropulsion or retropulsion of urethral stones is preferred over attempts to push urethral stones back into the bladder using a urinary catheter. General anesthesia is usually required for retropulsion. If the bladder is overdistended, decompressive cystocentesis (using a 22-gauge needle connected to a 60-mL syringe by extension tubing and a three-way valve) is performed and fluid therapy should be administered to correct acid–base and electrolyte imbalances before anesthesia. The largest urinary catheter possible is gently passed up to the level of the distal urolith. An assistant compresses the urethra against the pubis via rectal palpation. A 2:1 mixture of sterile saline and sterile aqueous lubricant is rapidly flushed into the urethra while compressing the urethral orifice around the catheter to prevent fluid leakage from the penis. An estimate of the total volume of flush required is 5 mL/kg of body weight or 60 mL, whichever is less. Once the urethra begins to dilate, the rectal compression is released while flushing continues. If the urethroliths pass retrograde, the catheter is gently advanced to the trigone. If the calculus does not move retrograde, the degree of bladder distention should be assessed prior to repeating the procedure. Subsequent retrograde flushes are done with sterile saline alone, because the urethra is well lubricated. Successful retrograde movement of the urethroliths should be confirmed by cystoscopy or radiography. The aim of retrograde urohydropropulsion is to flush the uroliths into the bladder, not to push them with the urinary catheter. Pushing against urethroliths with rigid polyethylene catheters may result in mucosal trauma, urethral perforation, or the catheter being passed round the urolith. Catheter-induced trauma predisposes to future urethral stricture formation.

LASER LITHOTRIPSY

In humans, laser lithotripsy using the holmium:YAG laser has become the technique of choice for fragmentation of large bladder calculi, ureteroliths and nephroliths. In our hospital, holmium laser lithotripsy has replaced other techniques for fragmentation of bladder stones. The holmium laser energy is absorbed in 0.5 mm of fluid, allowing it to safely fragment uroliths within the urethra or ureter. With the small diameter of the laser fibers, laser lithotripsy can be performed through small diameter flexible endoscopes as well as larger rigid cystoscopes. Recent in vitro studies confirm that the holmium laser can efficiently fragment uroliths from dogs regardless of chemical composition. Davidson et al showed that implanted urethroliths could be safely fragmented with minimal trauma to the urethral mucosa.

Our initial experience with laser lithotripsy using the holmium laser has been excellent. When working through the biopsy channel of rigid cystoscope, we use a 550 micron fiber to deliver the laser energy to the surface of the urolith. Both 200 and 365 micron fibers work well through the 3-French working channel of a flexible endoscope, although care must be used to avoid damaging the working channel with the rigid tip of the fiber. Care must be used to flush the urolith "dust" out of the field to maintain visualization during laser lithotripsy. Laser lithotripsy using the holmium laser is available at Purdue University, the University of Minnesota, University of Pennsylvania, VA-MD Regional CVM, Michigan State University, and University of California-Davis as well as some private referral hospitals. As holmium lasers become more widely available in veterinary medicine, this technique has the potential to replace open cystotomy and urethrotomy for removal of uroliths in referral hospitals. Laser lithotripsy has the advantage of being a non-surgical procedure with minimal healing time. Most dogs are clinically normal within 12 to 24 hours of the procedure.

MANAGEMENT OF UROLITH RECURRENCE

Calcium oxalate uroliths tend to recur in most dogs with recurrence rates of up to 50% within 3 years of initial diagnosis. Therefore preventative measures such as diet and medications should be utilized to reduce the risk of recurrence. Dietary changes should be attempted, and the clinician should add medications if there is persistence of calcium oxalate crystalluria or recurrence of calcium oxalate urolithiasis is noted. Increased water intake though feeding a canned diet or by adding water to the diet may be the most important recommendation to help prevent recurrence of calcium oxalate urolithiasis in dogs.

Although diets designed for dogs with renal failure have been recommended previously for prevention of calcium oxalate urolithiasis, because these diets are phosphorus restricted, I do not recommend their use for this purpose. Reduced dietary phosphorus was associated with increased risk of calcium oxalate urolithiasis in dogs. Dietary phosphorus restriction promotes increased intestinal absorption of calcium with the excess calcium excreted in the urine. Deficient dietary phosphorus also increases renal production of calcitriol which promotes intestinal absorption of calcium and phosphorus. Additionally, increased dietary intake of phosphorus is thought to increase urinary excretion of pyrophosphate, an inhibitor of calcium oxalate crystallization.

The commercial diets most often recommended to reduce the risk of calcium oxalate urolithiasis include Royal Canin Canine S/O Lower Urinary Tract Support Diet and Hill's Prescription diet u/d. Diets with high fat content such as Prescription diet u/d should be avoided in dogs with history of pancreatitis, obesity, diabetes mellitus or hyperlipidemia. An alternative diet suggested for these patients is Hill's Prescription diet w/d with supplementation of oral potassium citrate to achieve a urine pH of 6.5 to 7.0.

Dietary therapy alone will not always prevent calcium oxalate urolith recurrence. Hydrochlorothiazide (2 mg/kg PO q 12 h) should be considered in dogs that have persistence of calcium oxalate crystalluria or recurrence of calcium oxalate urolithiasis despite diet therapy. Thiazide diuretics cause subclinical volume depletion resulting in increased proximal tubular reabsorption of sodium and calcium. Once dietary and hydrochlorothiazide therapy have been implemented, if calcium oxalate crystalluria is persistent or calcium oxalate uroliths recur, potassium citrate should also given to effect to achieve a urine pH of 6.5 to 7.0 using a starting dose of 50 to 75 mg/kg PO q 12 hours. If the urine pH is already above 7.0 to 7.5, then potassium citrate should not be added. The serum potassium should be initially monitored monthly during potassium citrate supplementation and the dose reduced if hyperkalemia occurs.

Because calcium oxalate uroliths commonly recur,[15] appropriate surveillance methods should be utilized to document recurrences before the uroliths become too large to pass through the urethra. If recurrent urocystoliths are diagnosed while small enough, many recurrences may be managed using nonsurgical methods such as voiding urohydropropulsion. Although some dogs with recurrent calcium oxalate urocystoliths may be asymptomatic for extended periods of time, removal of urocystoliths is recommend to prevent urethral obstruction.

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NEW TECHNIQUE FOR TREATMENT OF ECTOPIC URETERS

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Urinary incontinence is defined as loss of voluntary control of urination resulting in leakage of urine from the urinary system to the exterior of the body. Ectopic ureters are a common cause of urinary incontinence in young dogs. Most canine ectopic ureters are intramural in location, meaning the ureter enters the serosal surface of the bladder wall in the correct location, but tunnel in the wall of the bladder and urethral submucosa with one or more openings in the urethra and/or vaginal vestibule. Extramural ectopic ureters connect to the urethra or vagina without first tunneling through the bladder and urethral wall.

The most sensitive technique for diagnosing ectopic ureters is cystoscopy (provided the clinician is experienced with the procedure). In one study, ectopic ureters were diagnosed correctly 75% of the time by excretory urography versus 100% with cystoscopy.[1] During cystoscopy, the anatomy of the urethra and vaginal vestibule are also evaluated. Most dogs with ectopic ureters have an abnormality of the vaginal vestibule called paramesonephric septal remnant which is a broad band dividing the vaginal opening into two parts and lifting the urethral opening dorsally.

Traditionally ureteral openings have been moved into the bladder by various surgical techniques. A new technique for treatment of intramural ectopic ureters is to use a diode laser to remove the wall between the urethra and parallel ureter. In an abstract presentation,[2] Dr. Berent reported that laser ablation of intramural ectopic ureters resulted in resolution of urinary incontinence in 5 of 8 female dogs and 4 of 4 male dogs for 6 months after laser correction. Additionally, 2 of 8 female dogs were continent with treatment with phenylpropanolamine or periurethral collagen injections. There is one additional single case report of successful resolution of urinary incontinence after laser ablation of an ectopic ureter in a female dog. We have been also successfully resolved urinary incontinence in several dogs by laser ablation of intramural ectopic ureters; although some dogs also require medical management with phenylpropanolamine or periurethral collagen injections to improve urethral function.

Urethral incompetence frequently occurs concurrently with ectopic ureters and can result in treatment failure if ectopic ureters are repaired by moving the ureteral opening into the urinary bladder. Because urethral pressure profile (UPP) results can be used to predict postsurgical continence, urodynamic testing should be performed prior to surgical correction or laser correction of ectopic ureters. Some dogs with concurrent urethral incompetence have improved continence after surgical correction if treated with phenylpropanolamine.

Periurethral injection of bulk-enhancing agents offers an alternative for cases of refractory urinary incontinence attributable to concurrent urethral incompetence. In humans, periurethral injections of glutaraldehyde cross-linked collagen (Contigen®) or other bulk-enhancing agents are used to treat urinary incontinence with minimal side effects. Collagen injections have also been used to control refractory urinary incontinence in female dogs.

Laser ablation of ectopic ureters offers a new minimally invasive option for treatment of urinary incontinence in dogs with intramural ectopic ureters. Augmentation of urethral function by medication or periurethral collagen injections is required for continence in dogs with concurrent urethral incompetence.

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WHAT WE KNOW ABOUT NSAIDs AND CAT KIDNEYS

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Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly prescribed for cats (and dogs) for the symptomatic treatment of acute and chronic pain conditions through inhibition of prostaglandin synthesis. The physiologic effects of prostaglandins are both hemodynamic and non-hemodynamic. The formation of prostanoids is mediated by one of two isoforms of cyclooxygenases. Cyclooxygenase 1 (COX-1) is generally thought of as the "housekeeping" isoform which mediates the formation of constitutive prostaglandins produced by many tissues. Cyclooxygenase 2 (COX-2) was originally viewed as an inducible form, being expressed primarily in the presence of inflammation.

RENAL EFFECTS OF NSAIDS

Inhibition of cyclooxygenase-2 produces some of the therapeutic effects of NSAIDs, which include anti-inflammatory, analgesic, and antipyretic properties. By this simple paradigm, the therapeutic effects of NSAIDs (eg, analgesia) are mediated by COX-2 inhibition and the toxic effects (eg, gastric ulceration and reduced renal function) are mediated by COX-1 inhibition. To the extent this approach is valid, differential inhibitory effects of NSAIDs on the isoforms of cyclooxygenase can provide therapeutic advantages.

In the feline kidney, prostaglandins have a variety of effects, including hemodynamic, hemostatic, and cytoprotective functions. Prostaglandins are important in renal function as they participate in the regulation of the renin-angiotensin-aldosterone system by promoting the release of renin from the kidney in response to extracellular fluid volume depletion. Prostaglandins also alter tubular handling of water and electrolytes, particularly in animals with reduced circulating blood volume.

The localization of isoenzymes of COX in the feline kidney is incompletely known. Both COX-1 and COX-2 are expressed in the canine kidney and play important roles in regulation of renal function. COX-1 is constitutively expressed in the collecting duct cells, medullary interstitial cells, endothelial cells, and smooth muscle cells of the pre- and postglomerular vessels and appears to play a role in hemodynamic regulation. Conventionally, COX-1 is believed to be important in producing vasodilatory prostaglandins which maintain renal plasma flow and glomerular filtration rate during conditions that otherwise favor renal vasoconstriction and depressed renal function. While renal expression of COX-2 was once thought to be inducible and up-regulated only in the presence of inflammation, it is constitutively expressed in the macula densa, the cortical thick ascending limb of the loop of Henle, and medullary interstitial cells. The physiologic and pathologic roles of this isoform are incompletely understood.

LOCALIZATION OF COX IN THE KIDNEY (Figure 1)

COX-1 (Constitutive)

- Endothelial cells, smooth muscle cells of the pre- and postglomerular vessels, glomerular mesangial cells (see 1 in Figure 1)
- Collecting duct cells, medullary interstitial cells (See 2; 4;5 in Figure 1)
- None in loop of Henle or macula densa

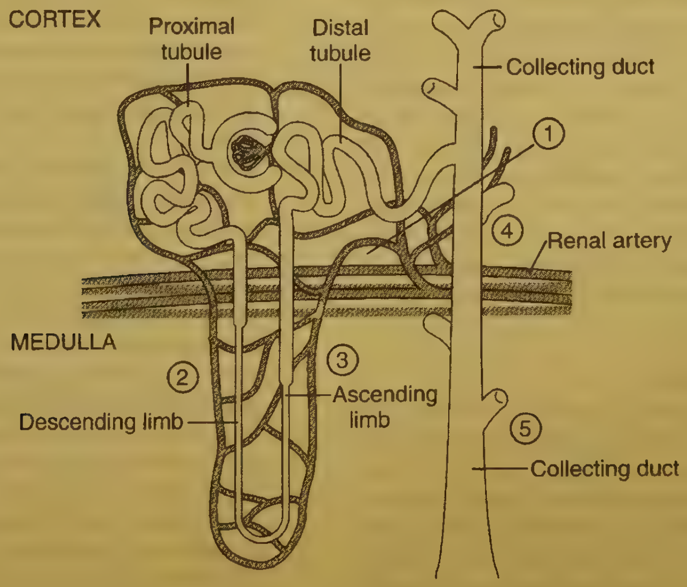

Figure 1. Localization of COX in the feline kidney.

COX-2 (inducible)

- Macula densa, thick ascending limb of loop of Henle, medullary interstitial cells (See 2;3;4;5 in Figure 1)
- Glomerulus (especially in diseased kidney)

HIGH RENIN STATES AND NSAIDS

In maintenance of renal blod flow, COX products and renin act in an antagonistic fashion. Whenever renin secretion is high, the formation of angiotensin II and aldosterone will tend to reduce renal blood flow and glomerular filtration rate (GFR). In this setting, COX fucntion is essential for renoprotection. Renal function is particularly dependent on COX function during this conditions known as high-renin states. Examples of high-renin states include:

- Extracellular fluid volume depletion
- Systemic hypotension
- Dietary salt restriction
- Chronic kidney disease
- Administration of angiotensin converting enzyme (ACE) inhibitors

NSAIDs AND ACE INHIBITORS

At the renal glomerulus, angiontesin II tends to reduce blood flow and local prostaglandin production acts to counteract this effect. Consequently, the administration of an NSAID to a cat in a high renin state (eg, systemic hypotension or dehydration) can lead to profound reductions of renal function. Cats, particularly those with kidney disease, are often treated with ACE inhibitors. In control of renal perfusion, prostaglandins and angiotensin II often serve this counter-regulatory role in a much more complex and unpredictable manner. Thus, inhibition of both systems can produce adverse effects on GFR and renal blood flow. In the worst case scenario, the administration of an ACE inhibitor will reduce blood pressure, and the loss of supportive local prostaglandin products can lead to dramatic reduction of blood flow and even acute tubular necrosis and acute renal failure. Thus, while there are clinical situations wherein co-administration becomes a reasonable consideration, this should be accomplished only with careful monitoring of serum creatinine concentration (evidence of substantial loss of renal function). and observation of the urinalysis for the presence of casts (evidence of tubular necrosis), proteinuria (evidence of renal injury), and low urine specific gravity (evidence of loss of renal function).

NSAIDs AND RENAL INJURY

In situations in which renal perfusion is prostaglandin-dependent, NSAID administration can cause immediate reductions in GFR and renal perfusion rate (RPF) and potentially may result in hypoxic injury to the kidney. Previous studies have established that renal prostaglandin dependence may be present during general anesthesia, extracellular fluid volume depletion and/or renal insufficiency. In each of these settings, the administration of an NSAID may reduce renal function and/or produce acute tubular necrosis. Ibuprofen, a propionic acid derivative that has been used in dogs, is classified as a nonselective COX inhibitor. Accordingly, ibuprofen has been associated with renal failure. The effects of an NSAID on GFR and RPF may be less severe if it selectively inhibits COX-2. Unfortunately, this is valid for some, but not all, COX-2–selective agents. This is due to a variety of factors, including the fact that COX-2 selectivity is species-, dose-, and tissue-dependent.

SUMMARY

- Feline chronic kidney disease is a PGE$_2$-dependent state
    - NSAIDs may reduce GFR
        - Administer NSAIDs with caution and only to well- hydrated animals
        - COX-2 selective agents could be less safe?
        - Measure serum creatinine/ urinalysis in 5 days
- ACE inhibitors enhance PGE$_2$-dependence
    - ACE inhibitors in normal cat: NSAIDs may reduce GFR
        - Administer NSAIDs with caution and only to well- hydrated animals
        - Measure serum creatinine/ urinalysis in 5 days
    - ACE inhibitors + CKD: NSAIDs may dramatically reduce GFR
        - Avoid if possible!
- Acute renal compromise is not predictable!
    - Inherent toxicity limited (GFR effects small in feline CKD)

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HOW DO I GET BETTTER PHOSPHORUS CONTROL IN DOGS AND CATS WITH CHRONIC RENAL FAILURE

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Total phosphorus burden/retention during chronic renal failure (CRF) adversely affects renal function, renal histopathology, and soft tissue mineralization. Dietary modification and intestinal phosphate binders are pivotal treatments to provide optimal phosphorus and parathyroid hormone (PTH) control. Compared with humans consuming an average diet, cats consume 6 times as much and dogs about 5 times as much dietary phosphorus when eating commercial maintenance foods. With such a high starting point, it is difficult to achieve the degree of phosphorus restriction that is targeted in human medicine.

Renal secondary hyperparathyroidism is commonplace in dogs and cats with IRIS stage 3 and 4 chronic kidney disease and can be documented in some with stage 2. Dietary phosphorus restriction in CRF has been shown to blunt or reverse renal secondary hyperparathyroidism in cats and dogs. Renal lesions in dogs and cats are less severe in experimental models when fed phosphate restricted renal diets. Survival times and GFR were also better in dogs and cats fed the phosphate-restricted diets. Extremely phosphorus-depleted diets are unpalatable (due to very low levels of protein needed to provide this phosphorus restriction). Diets moderately restricted in phosphorus may provide adequate phosphate control (normal serum phosphate and PTH) during early stages of chronic renal failure. Diet alone is not successful in adequate phosphorus control as chronic renal disease becomes more advanced. In these instances, serum phosphorus concentration increases above the normal range or stays in the upper half of the normal range.

When CRF is diagnosed, phosphorus restriction is initiated by feeding a low phosphorus, low protein diet. Renal diets achieve phosphate restriction largely by restriction of dietary proteins that contain phosphorus, especially animal origin proteins. Renal diets may be successful in control of serum phosphorus into the normal range, but this does not guarantee that PTH has returned to the normal range. In a recent report of renal diets in dogs with CRF and another in cats with CRF, dietary intervention alone failed to control PTH.

If necessary, oral phosphorus-binding agents can be added to the treatment regimen to provide additional reduction in serum phosphorus and PTH concentration. All intestinal phosphate binders work best when given with food. Due to varying effects of intestinal phosphate binders to limit absorption of drugs, it is advisable to give other drugs 1 hour before or 3 hours after any intestinal phosphate binder is given. Phosphorus-binding agents are given orally to trap phosphorus in the gut and increase its excretion into feces. These drugs should be given with meals or within 2 hours of feeding to maximize their binding of dietary phosphorus. The goal is to increase fecal excretion of phosphorus by not allowing its GI absorption.

Aluminum hydroxide (Amphojel®) initially is used at a dosage of 30 mg/kg q8h or 45 mg/kg q12h given with food. An attempt should be made to maintain serum phosphorus <6.0 mg/dL. Constipation is the most common side effect encountered during treatment with aluminum phosphate binders, especially in cats. Lactulose treatment helps alleviate constipation in these instances.

Calcium carbonate also may be used at a starting dosage of 30 mg/kg q8h or 45 mg/kg q12h given with food. Calcium-based intestinal phosphate binders were developed for use in human medicine due to concerns about long-term effects of aluminum accumulation. Calcium acetate is more effective than other calcium-containing phosphorus binders and may be used at a slightly lower dosage. It is comparable to aluminum based phosphate binders. Calcium acetate also results in less hypercalcemia than during the use of calcium carbonate. Hypercalcemia is more likely when used with calcitriol. Doses of 20, 30, or 40 mg/kg with each meal approximate doses recommended for humans with dialysis dependent CRF. Animals should be monitored for development of hypercalcemia whenever calcium-containing phosphorus binders are used. The development of hypercalcemia is much more of a problem with calcium salts are used at the same time that calcitriol treatments are being given (non-calcium containing salts are preferred during calcitriol or activated vitamin D metabolite treatment).

Sevelamer HCl is a relatively new phosphorus binder used in human patients on dialysis. Its effects on dogs and cats with clinical CRF have not been reported. Sevelamer is an organic polymer that does not contain aluminum or calcium and is not systemically absorbed. It is hydrophilic but not soluble in water. Pills should be given intact; since sevelamer is hydrophilic it will expand in water. Sevelamer may be associated with gastrointestinal side effects including constipation. At extremely high dosages (6 to 100 times the recommended dosage in humans) sevelamer may be associated with impaired absorption of folic acid and vitamins K, D, and E.

Lanthanum carbonate was developed as a non-aluminum and non-calcium-containing intestinal phosphate binder. It appears to be a very effective intestinal phosphate binder. Free lanthanum ions become available following exposure of lanthanum carbonate to the acidic environment of the stomach. Highly insoluble lanthanum phosphate complexes develop which are not absorbed across the GI tract. Very little lanthanum is absorbed across GI tract in humans. Lanthanum appears to have minimal toxicity in humans, but it has been in use for a short time. There are no reports of its clinical use in dogs or cats. Toxicity studies in dogs show that lanthanum increases in many tissues (especially GI tract, bone and liver) during treatment. Tissue levels remained high for longer than 6 months in dogs following discontinuation of treatment.

Epakitin® (Vetoquinol) is marketed as a neutracetuical on the veterinary market. It contains the adsorbent chitosan (8% crab and shrimp shell extract) and 10% calcium carbonate. The digestibility of dietary protein and phosphorus was reduced when administered to cats with CRF. Its beneficial effects in clinical animals with CRF have yet to be demonstrated. Hypercalcemia occasionally results during treatment.

If the patient is not hyperphosphatemic at the time of initial evaluation, phosphorus restriction still may be beneficial in reversing existing renal secondary hyperparathyroidism. Fractional excretion of phosphorus can be monitored but is not a very sensitive indicator of renal hyperparathyroidism. All serum phosphorus determinations should be made in the fasting state. Serial PTH determinations are an ideal but costly way to monitor treatment of renal hyperparathyroidism.

WHAT'S NEW WITH FELINE RENAL DISEASE

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Ureteral obstruction from calcium oxalate ureteroliths or nonmineralized debris has become one of the most significant causes of renal disease and acute uremia in cats over the past 10 to 15 years. Although greater awareness and imaging techniques have contributed to its increased identification in recent years, there is little doubt that this represents a new clinical entity in cats. The clinical presentation depends on the completeness and duration of the ureteral obstruction and the number of kidneys affected.

ACUTE UNILATERAL URETERAL OBSTRUCTION

Generally, unilateral ureteral obstruction is clinically silent, potentially transient, and not associated with azotemia. Evidence of unilateral obstruction may be detected in cats presented for signs of acute abdominal pain, erratic or elusive behavior, or on routine abdominal imaging.

ACUTE BILATERAL URETERAL OBSTRUCTION

This presentation is uncommon but associated with severe acute signs including bilaterally enlarged and painful kidneys, severe progressive azotemia, and oliguria or anuria. Prognosis is good if the obstructions are alleviated because renal mass is intact, but reoccurrence may be common.

BIG KIDNEY-LITTLE KIDNEY SYNDROME

This common presentation is seen in cats with a past unilateral ureteral obstruction that has caused the kidney to progress to a fibrotic end-stage. Subsequently, the contralateral, hypertrophied kidney becomes acutely obstructed by a ureterotith causing the further enlargement and renal asymmetry, abdominal pain, progressive severe azotemia, and variable urine production. Prognosis is good if the obstruction is alleviated because adequate renal mass persists, but reoccurrence in the big kidney is common.

BILATERAL CHRONIC KIDNEY DISEASE WITH CONCOMITANT URETERAL OBSTRUCTION

This presentation is common and carries the most guarded prognosis because even with resolution of the ureteral obstruction, global renal function is severely compromised, and there may be little capacity for renal repair. The underlying chronic kidney disease may be secondary to fibrotic changes from previous ureteral obstruction or other intrinsic kidney diseases which may predispose urolith formation. The sudden obstruction (unilateral or bilateral) causes decompensation of the tenuous residual renal function and promotes the onset of overt uremia.

The usual clinical presentation ureteral obstruction is for signs of severe acute uremia which include anorexia, depression, intermittent vomiting, uremic odor, lethargy, weight loss, and oligoanuria which can be differentiated easily from other causes of acute uremia. The syndrome may occur in cats of all ages, but appears to be more prevalent in cats older than 7 years of age. Affected cats may have a previous history of calcium oxalate urolithiasis or an entirely unremarkable history. The uremia is readily confirmed by serum chemistries documenting profound azotemia (serum creatinine concentration >7 mg/dL), metabolic acidosis, hyperphosphatemia, and variable hyperkalemia. Cats may present with dehydration or life-threatening overhydration depending on management prior to presentation. On abdominal palpation, the kidneys are asymmetrically or symmetrically enlarged or small according to the presentations indicated above. They are characteristically resilient but firm, smooth or irregular, and painful. The bladder may or may not contain urine. Interestingly, many cats with ureteral obstruction and severe uremia often display a clinical demeanor that is considerably better than that of similarly uremic cats of other etiologies. Many cats are uncharacteristically aggressive and discontented due to pain associated with the condition.

The diagnosis of ureteral obstruction is made on the basis of physical findings and clinical suspicion and is confirmed by abdominal imaging. Survey radiography and ultrasonography are highly complimentary imaging modalities and both are indicated in the evaluation of every cat with acute uremia. Ultrasonography provides greater delineation of renal geometry, intrarenal architecture, parenchymal consistency, and outflow integrity than survey radiography but its sensitivity is only 70% to 80% for the diagnosis of ureteral obstruction. Hydronephrosis and dilation of the proximal ureter are the principal sonographic features of ureteral obstruction. However, clinical experience has demonstrated that these findings may be not be demonstrated for up to 4 to 7 days following complete obstruction of the distal ureter (personal observations). The increased availability and utility of ultrasonography have curtailed the routine use of survey radiography to image the urinary tract, and this trend has likely delayed the broader recognition of this condition over the past 5 to 10 years. Survey radiographs may be more sensitive and predictive than ultrasonography for the diagnosis of ureteral obstruction in cats if careful scrutiny is directed to barely perceptible radiodensities in the retroperitoneal space, expansion of the retroperitoneal space, and the presence of marked renal asymmetry. In 20% to 30% of cats with ureteral obstruction, no discrete calcific material is identified with either ultrasound or survey radiographs. For these circumstances, and for cases with multiple sites of obstruction or stenosis, antegrade pyelography or computed tomography can be used to define the indication and location for surgical intervention. Antegrade pyelography incorporates ultrasound-guided pyelocentesis and antegrade injection of positive radiographic contrast media into the renal pelvis and ureter to radiographically delineate the size of these structures and the patency of the ureter. Antegrade pyelography can be performed in specialty practice and reliably confirms the presence, degree and location of ureteral obstruction in cats. Computed tomography with contrast is a less invasive than antegrade pyelography and equally useful to confirm mineralized uroliths and differential patency of the ureters. This is especially useful if the cat has bilateral ureteroliths, but these facilities are not as readily available.

The management of acute ureteral obstruction is directed primarily at stabilizing the clinical consequences of the oligoanuria and uremia and secondarily to alleviate the obstruction and reestablish renal function. After the ureteral patency has been established by spontaneous passage of the obstructing urolith or surgical resolution, therapeutic attention must be directed to prevention of future occurrences of calcium oxalate urolith formation. Two dietary approaches have been proposed to reduce calcium oxalate recurrence, with both approaches reliant on reduction of the relative supersaturation potential for calcium oxalate. One approach focuses on the controlled reduction of dietary substrates for calcium oxalate nucleation and urinary pH control to lower the relative supersaturation potential. The alternative approach purports to control the potential for spontaneous homogeneous crystallization of calcium oxalate through contrived urinary dilution with the addition of increased dietary salt and controlled urinary pH. The efficacy of both theoretically conceived approaches await controlled therapeutic trial in predisposed or affected cats, and neither approach can be endorsed explicitly or preferentially at this time.

Controversy has evolved over the potential risks of the use of dietary salt to increased water consumption, urine formation, and urinary dilution to reduce the relative supersaturation for calcium oxalate and struvite. Therapeutic increases in dietary salt intake have been implicated in alterations in body fluid volume and progression of chronic kidney disease in cats. To date, there has not been convincing evidence that cats with normal kidney function or cats with chronic kidney disease are harmed by this approach. At the foundation of the concern for the use of therapeutic salt intake is the potential for expansion of body fluid volume and increases in blood pressure to promote systemic hypertension. Several recent studies have addressed this potential, but the employed methodologies using indirect blood pressure measurements are not likely to be sensitive enough to document changes in blood pressure. To provide clarity to this controversy, we recently investigated the potential for increases in dietary salt at levels suggested for calcium oxalate urolith prevention to influence body fluid composition, systemic blood pressure, and renal function.

We investigated a group of 6 cats with normal kidney function who were fed either a commercial diet containing 0.22% sodium (as fed) or the identical diet supplemented with salt to 1.3% sodium (as fed). Two groups of three cats were randomly fed one of the two diets for 4 weeks then all cats were transitioned to the low-sodium diet for 4 additional weeks before crossing over to the alternative diet for 4 weeks. Compared with the 0.22% sodium diet, when animals were the fed the 1.3% sodium diet, they consumed approximately 10% less diet, ingested 5.5 times as much dietary sodium (150 mg/day to 825 mg/day), and lost 8% body weight. Interestingly, 1.3% sodium diet caused a significant decrease in serum creatinine and BUN despite no identifiable change in the plasma clearance of exogenous creatinine as a marker of GFR. Total CO_2 increased significantly during high sodium intake.

Body fluid composition (extracellular fluid volume, intracellular fluid volume, and total body water) was assessed weekly with multifrequency bioimpedance spectroscopy. When cats ate the 1.3% sodium diet, extracellular fluid volume increased significantly from 21.2% of body weight (0.22% sodium) to 23.8% of body weight consistent with ECF volume expansion in response to dietary sodium. These reflect modest changes in volume, but the time frame was only 4 weeks and the long-term clinical significance is not apparent from this study.

Changes in systemic blood pressure represent the assessment of most recent concern and interest in relation to feeding high-sodium-containing diets. One of the most important considerations for interpretation of previous and future reports investigating the influence of dietary salt on blood pressure is the volatile nature of feline blood pressure and the likelihood that conventional, indirect techniques are sufficiently sensitive to document changes within the minute-to-minute variance of the pressure in this specie. Figure 1 illustrates changes in systolic blood pressure in a cat averaged over 10-second intervals for greater than 90 days (upper panel) or more narrowly over 48 hours (insert, lower panel) as recorded with an intra-arterial telemetric blood pressure implant. It is evident from this figure that systolic blood pressure could be as low as 120 mmHg one minute and greater than 200 mmHg a minute later. The pressure recorded and the interpretation of dietary effects on blood pressure may be entirely dependent on which minute the pressure is measured. Even when averaged over 5 to 10 minutes characteristic of clinical or investigative assessments, the intrinsic variance likely would preclude identification of clinically or statistically significant changes. More exacting blood pressure assessments free from environmental influences and the volatility of short-term variations can be determined by application of ambulatory, unobtrusive measurement techniques and time-averaging transformations afforded with the radiotelemetric methods. As illustrated in Figure 2, time filtering (1 hour) and time-averaging permit assessment of a stable pressure measurement which represents the "physiologic consensus" over a defined time interval. These measurements also are obtained without the artifacts associated with the stress and anxiety of the measurement procedures. With these sensitive techniques, feeding the high-sodium diet produced a highly statistically significant 4% to 7% increase in systolic, diastolic, and mean blood pressure compared with feeding the low-sodium diet. The clinical significance of these short-term and modest changes in

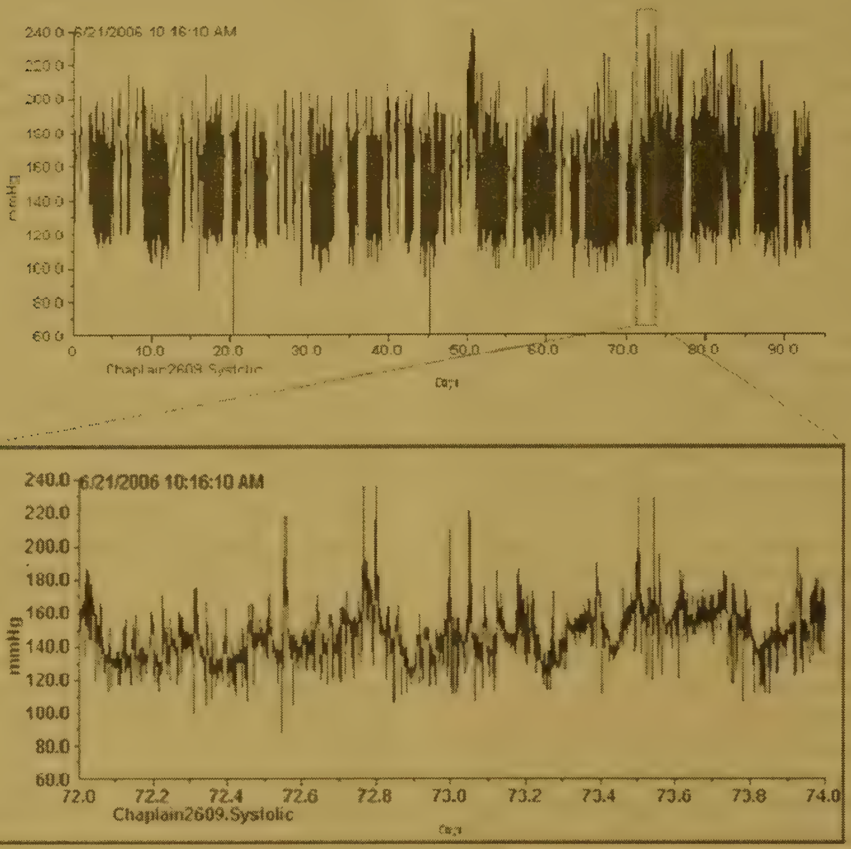

Figure 1. Continuous, plot of systolic blood pressure in a cat with a radiotelemetric blood pressure implant in the femoral artery (upper panel). The data reflect systolic blood pressure averaged over 10-second intervals of observation for greater than 90 days (lower panel). The insert in the lower panel demonstrates the same 10-second averages for systolic blood pressure displayed over an expanded 48-hour interval between day 72 and day 74. The straight line through the curve represents the continuous time-averaged systolic blood pressure over the 48-hour interval.

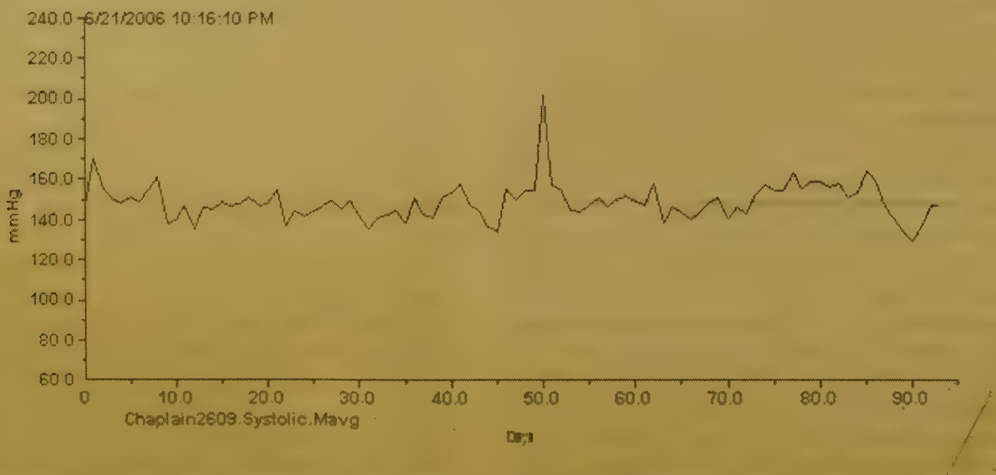

Figure 2. Same systolic blood pressure measurements as in Figure 1 averaged over 1 hour to decrease the minute-to-minute variation in cat blood pressure. The horizontal line represents the ambulatory time-averaged systolic pressure over the entire 90-day period of observation.

blood pressure remains unknown, but would not have been noticed or detectable with conventional blood pressure methodologies.

Ureteral obstruction is an increasingly recognized feline disease with the likelihood of a dietary etiology and profound immediate and long-term consequences. It requires accurate and immediate recognition and a coordinated medical, dialytic, and surgical approach to save cats that are most severely affected. Subsequent to the management of its acute and life-threatening manifestations, long-term dietary approaches designed to prevent reoccurrences have been advocated. The therapeutic use of dietary salt is the basis of one approach to prevent recurrent calcium oxalate ureteroliths, but its indiscriminate application to all cats and particularly cats with occult or overt chronic renal disease or heart disease has been challenged. We have documented that increases in dietary sodium to 1.3% (as fed) can promote modest decreases in body weight and modest ECF volume expansion and increased blood pressure as predicted short-term adaptations. These short-term observations and their physiologic or clinical significance remain unknown for cats with normal renal function or chronic kidney disease. Our observations further document that 1.3% dietary sodium caused no short-term alteration in GFR and appears to be safe in cats with normal renal function. Clearly, there is need for long-term, carefully controlled clinical trials for all dietary strategies to document both efficacy and safety in predisposed cats with both normal and compromised renal function before there can be rational therapeutic recommendation and risk assessment.

MATURE MYSTERIES: OLD AGE AIN'T NO PLACE FOR SISSIES — MANAGING OSTEOARTHRITIS IN PATIENTS WITH RENAL OR HEPATIC IMPAIRMENT

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Chronic kidney disease (CKD) is a common problem that affects an estimated 0.5% to 7% of dogs. Radiographic signs of osteoarthritis (OA) occur in 20% of dogs. The majority of OA and CKD are acquired and both conditions are more prevalent in older dogs. Use of nonsteroidal anti-inflammatory drugs (NSAIDs) has dramatically improved the quality of life for many dogs with OA. The potential nephrotoxicity of NSAIDs, however, make their use problematic in dogs with CKD. Thorough evaluation of renal function prior to the use of NSAIDs and follow-up monitoring for any adverse effects on renal function is extremely important in the older dog. Newer evidence suggests that the cyclo-oxygenase (COX) 2 enzyme is important in maintaining renal blood flow (RBF) in dogs and therefore, COX 2 selective/specific NSAIDs at least have the potential to adversely affect renal function in dogs. In contrast, the hepatotoxicity associated with NSAIDs in dogs appears to idiosyncratic and unrelated to the COX selectivity of the drug.

POTENTIAL NEPHROTOXICITY OF NSAIDs

Renal damage and disease can be caused by acute or chronic insults to the kidney. The terms *renal disease* and *renal damage* are used to denote the presence of renal lesions; these terms, however, imply nothing about renal function or the cause, distribution, or severity of the renal lesions. Acute renal damage (ARD) often results from ischemic or toxic insults and usually affects the tubular portion of the nephron. Early detection of ARD facilitates appropriate intervention that can arrest or at least attenuate tubular cell damage and the development of established acute renal failure (ARF). In contrast, nephron damage associated with CKD is usually irreversible and can be progressive. Pre-existing CKD increases the risk of ARD associated with the use of potentially nephrotoxic drugs.

Renal prostaglandins help regulate RBF and glomerular filtration rate (GFR), renin release, and sodium excretion. Potential adverse effects of renal prostaglandin inhibition with NSAIDs can include decreased RBF and GFR, hypertension, salt retention and edema.[1] Since both COX-1 and COX-2 enzymes are present/expressed in the canine kidney, any NSAID, regardless of its COX specificity or sparing properties, has the potential to produce adverse renal effects. In particular, dogs express higher basal levels of COX-2 in the kidney than some other species and may be uniquely sensitive to the nephrotoxic effects of COX-2 selective drugs. Although a number of studies have shown no adverse effects of the commonly used NSAIDs in dogs with normal kidneys, increased BUN and creatinine are common adverse events listed for NSAIDs at the FDA Adverse Drug Event Web site. Dogs in field trials of deracoxib and firocoxib had increased BUN at the end of the trials, while dogs treated with etodolac did not. In cases where RBF is decreased (eg, dehydration and decreased cardiac output), the vasodilatory effects of renal prostaglandins are critical and the potential for adverse effects associated with NSAID use is increased. There is also concern that patients treated with drugs that can decrease GFR (such as angiotension-converting enzyme (ACE) inhibitors) may have increased renal toxicity when treated with NSAIDs. Studies of elderly human patients have confirmed this effect, but in a study of normal dogs treated with enalapril and tepoxalin no alteration of GFR was noted.[7]

RISK FACTORS FOR ACUTE RENAL DAMAGE

Dehydration and volume depletion are perhaps the most common and most important risk factors for development of ARD/ARF. Hypovolemia not only decreases renal perfusion, which can enhance ischemic damage, but also decreases the volume of distribution of potentially nephrotoxic drugs. In addition to hypovolemia, renal hypoperfusion may be caused by decreased cardiac output, decreased plasma oncotic pressure, increased blood viscosity, systemic hypotension, and decreased renal prostaglandin synthesis. Any of these conditions can increase the risk of ARD associated with the use of NSAIDs.

Pre-existing renal disease can increase the potential for nephrotoxicity and ischemic damage by several mechanisms. The pharmacokinetics of potentially nephrotoxic drugs can be altered in the face of decreased renal function. Gentamicin clearance is decreased in dogs with subclinical renal dysfunction, and the same is probably true for other nephrotoxicants that are excreted via the kidneys. Animals with renal insufficiency also have reduced urine concentrating ability and, therefore, decreased ability to compensate for prerenal influences. Renal disease may also compromise the local production of prostaglandins that help maintain renal vasodilatation and blood flow. Age has been identified as a risk factor because many geriatric dogs have pre-existing renal lesions and subclinical loss of renal function.

USE OF NSAIDs IN DOGS WITH CHRONIC KIDNEY DISEASE

In dogs with pre-existing renal disease, the use of NSAIDs has the potential to exacerbate the renal disease and further decrease renal function and therefore NSAIDs should be avoided whenever possible in such animals. Certainly, the more advanced the stage of CKD, the greater the relative contraindication for the use of NSAIDs. It is important to remember that as early as stage II, more than 75% of the patient's nephrons are no longer functional and the patient's ability to autoregulate RBF is compromised.

Hypertension and proteinuria are commonly associated with CKD and proteinuria has been associated with progressive decline of renal function in CKD patients. Angiotensin-converting enzyme inhibitors (ACEI) are commonly used in dogs with hypertensive and/or proteinuric CKD as renoprotective treatments. In addition to inhibiting the conversion of angiotensin I to angiotensin II, ACEI decrease the degradation of kinins, which exert a vasodilatory effect on renal vessels by way of prostaglandin production. NSAID treatment in a patient already receiving an ACEI has the potential to decrease the efficacy of the ACEI by inhibiting prostaglandin production. NSAID interference with ACEI is agent, dosage, and species specific and effects in dogs are largely unknown, however in a study of healthy dogs being treated with either enalapril or benazepril, tepoxalin did not alter renal blood flow or glomerular filtration rate.

Recommendations surrounding the use of NSAIDs in CKD patients are largely speculative, but practical suggestions include:

- Maintain good hydration in these patients at all times
- Increase the monitoring of these patients for early signs of ARD
- Increase the monitoring of these patients for hypertension
- Use the lowest efficacious dose of a NSAID
- Use analgesic drugs with less renal toxicity in place of NSAIDs
- Monitor quality of life indices on a regular basis

In people, small stable increases in BUN and creatinine are often tolerated in rheumatoid and osteoarthritis patients on NSAIDs, because no other drugs maintain adequate quality of life.

EARLY RECOGNITION OF ACUTE RENAL DAMAGE

Numerous urine parameters can herald the development of ARF in patients with initially normal renal function. The value of monitoring these parameters in CKD patients receiving NSAIDs has not been assessed. Increased urine turbidity or changes in urine sediment (increasing numbers of renal epithelial cells or cellular or granular casts) are other indications of acute renal damage along with increased excretion of sodium and chloride. The acute onset of tubular glucosuria (normoglycemic glucosuria) or the acute onset or increases in proteinuria may also be indicative of ARD. The interpretation of all of the above parameters is enhanced by knowledge of baseline values.

Detection of enzymes in the urine such as gamma-glutamyl transpeptidase (GGT) and N-acetyl-beta-D-glucosaminidase (NAG) has proven to be a sensitive indicator of early renal tubular damage. These enzymes are too large to be normally filtered by the glomerulus, and, therefore, enzymuria indicates cell leakage, usually associated with tubular epithelial damage or necrosis. Urinary GGT originates from the proximal tubule brush border and NAG is present in proximal tubule lysosomes. In studies of gentamicin-treated dogs, increased urinary GGT and NAG activity was one of the earliest markers of renal damage/dysfunction. Interpretation of enzymuria is aided by baseline values obtained prior to a potential renal insult; 2 to 3-fold increases over baseline suggest significant tubular damage. Urine enzyme/creatinine ratios have been shown to be accurate in dogs prior to the onset of azotemia obviating the need for time urine collections.

POTENTIAL HEPATOXICITY OF NSAIDs

Hepatocellular toxicosis associated with administration of carprofen has been reported in a retrospective study of 21 dogs. Thirteen of these dogs were Labrador retrievers. The most common clinical signs were anorexia, vomiting, lethargy, and diarrhea. All of the dogs had elevations in serum ALT, 20 had elevations in serum ALP, and 18 were hyperbilirubinemic. The elevations in serum ALT were greater than the elevations in serum ALP in 16 dogs. Eighteen of the dogs had histologic evidence of hepatic necrosis characterized by multifocal to extensive vacuolar change, lytic necrosis, and apoptosis. It is interesting to note that 7 of 9 dogs evaluated by urinalysis had changes ranging from mild to severe proteinuria, normoglycemic glucosuria, and/or renal epithelial cells and casts in the urine sediment. Four of the affected dogs died or were euthanized within 3 to 5 days of presentation (all of the Labrador retriever dogs survived). The authors speculated that an idiosyncratic hepatopathy that may have been caused by the interaction of glucuronide metabolites of the acidic NSAID with plasma and hepatocellular proteins; resulting in the formation of antigenic NSAID-altered proteins causing immune-mediated damage to the liver.

EARLY RECOGNITION OF HEPATIC DAMAGE

NSAID-associated hepatoxicity appears to be a sub-acute toxicity (within 2–3 weeks of initiation of treatment) and unrelated to the type (COX selectivity) of the NSAID. Baseline liver enzyme values should be established prior to treatment. Post treatment, any anorexia, vomiting, lethargy, or diarrhea should prompt NSAID discontinuation and re-assessment of liver enzymes compared with baseline values. In dogs that remain clinically normal, reassessment of liver enzymes should be performed between 2 and 3 weeks after the NSAID treatment is started. If pretreatment assessment reveals mild to moderate elevations in liver enzymes, pre- and postprandial bile acid concentrations should be measured. Most authors state that an elevation in liver enzyme in the absence of liver dysfunction is not a risk factor for NSAID-associated hepatotoxicity. In dogs with reduced liver function, NSAIDs should be avoided, if at all possible.

Recommendations surrounding the use of NSAIDs in patients with decreased liver function are largely speculative, but practical suggestions include:

- Maintain good hydration in these patients at all times

- Increase the monitoring of these patients for early signs of hepatotoxicity
- Use the lowest efficacious dose of an NSAID/increasing the interval between doses
- Use alternative analgesic drugs in place of NSAIDs

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MANAGEMENT OF PROTEINURIA AND HYPERTENSION ASSOCIATED WITH CHRONIC KIDNEY DISEASE

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By altering pre-glomerular resistance, healthy kidneys can maintain relatively static glomerular capillary pressures despite variations in systemic blood pressure. This process is termed *renal autoregulation*. Renal disease and loss of nephrons can blunt this autoregulation allowing high systemic blood pressure to be transmitted to glomerular capillaries. For example, glomerular hypertension has been documented by micropuncture studies in dogs and cats with surgically reduced renal mass. In these models, glomerular hypertension was associated with glomerular hypertrophy, sclerosis, and proteinuria. Systemic hypertension is relatively common in dogs with renal disease. In a recent study of dogs with spontaneous chronic kidney disease (CKD), 29/45 (64%) had systolic blood pressure ≥ 144 mmHg and 14/45 (31%) had systolic blood pressure ≥ 161 mmHg. In cats with naturally occurring CKD, systemic hypertension has been observed in 19% to 65% of cases.

Glomerular proteinuria can result from immune complex disease or structural abnormalities involving the glomerular capillary wall (eg, x-linked hereditary nephropathy of male Samoyeds). Protein-losing nephropathy caused by glomerular capillary wall lesions is often accompanied by systemic hypertension. Proteinuria can also arise as a consequence of intraglomerular glomerular hypertension. Whether caused by capillary wall lesions or intraglomerular hypertension, excessive quantities of protein in the glomerular filtrate can cause additional glomerular lesions as well as tubulointerstitial lesions leading to loss of more nephrons. Therefore, it is difficult at times to separate the effects of high pressure and proteinuria.

CHRONIC KIDNEY DISEASE

The cause of canine and feline CKD is usually difficult to determine. Due to the interdependence of the vascular and tubular components of the nephron, the end point of irreversible glomerular or tubular damage is the same. Morphologic heterogeneity between nephrons exists in CKD with changes ranging from severe atrophy to marked hypertrophy. The histologic changes are not process specific. Renal diseases that have been associated with the development of CKD in dogs and cats include glomerulonephritis, amyloidosis, tubulointerstitial disease, pyelonephritis, nephrolithiasis, polycystic kidney disease, feline infectious peritonitis, and neoplasia. Progressive diseases that destroy nephrons at a slow rate allow intact nephrons to undergo compensatory hypertrophy, which can delay the onset of renal failure. When renal failure finally occurs, nephron hypertrophy can no longer maintain adequate renal function. Because of compensatory nephron hypertrophy, less than 25% of the original nephron population is functional when mild azotemia is present. In the later stages of the disease, less than 5% to 10% of the patient's nephrons may be functional.

The pathophysiology of CKD can be considered at both the organ and systemic level. At the level of the kidney, the fundamental pathology of CKD is loss of nephrons and decreased glomerular filtration. Reduced glomerular filtration results in increased plasma concentrations of substances that are normally eliminated from the body by renal excretion. In addition to excretion of metabolic wastes and maintenance of fluid and electrolyte balance, the kidneys also function as endocrine organs and catabolize several peptide hormones. Therefore, hormonal disturbances also play a role in the pathogenesis of CKD. For example, decreased production of erythropoietin contributes to the nonregenerative anemia of CKD and decreased metabolism and excretion of parathyroid hormone and gastrin contribute to osteodystrophy and gastritis, respectively. Finally, part of the pathophysiology of CKD is brought about by compensatory mechanisms like the hyperparathyroidism that develops in an attempt to maintain normal plasma calcium and phosphorus concentrations. Similarly, the individual glomerular filtration rate of intact nephrons increases in CKD in an attempt to maintain adequate renal function; however, proteinuria and glomerulosclerosis may be consequences or "trade-offs" of this hyperfiltration.

HYPERTENSION

Systemic hypertension in animals has largely been thought to be secondary to another disease (eg, renal disease and endocrinopathies), as opposed to idiopathic (primary, essential), as is the case in most human hypertensives. This has recently been called into question. For example, in a report of 69 hypertensive cats, seen at North Carolina State University (NCSU) for ocular disease, revealed that at least 17%, and possibly as many as 50%, of cats had no identifiable cause for their systemic hypertension suggesting that they had primary or essential hypertension. Elliott and associates at the Royal Veterinary College in London showed that approximately 20% of hypertensive cats, diagnosed in "primary-care" practice, were idiopathic. Another retrospective study, which used very strict criteria for the diagnosis of primary (essential, idiopathic) hypertension, revealed a prevalence of 11%.

Described and potential etiologies of secondary hypertension include acute and chronic renal disease, hyperthyroidism, hypothyroidism, hyperadrenocorticism, hyperaldosteronism, pheochromocytoma, diabetes mellitus, and obesity. Clearly, CKD has the greatest association with hypertension and may often be causal. A recent report suggested approximately 29% of elderly cats with CKD were hypertensive, with the range reported in four studies being 19% to 65%. In dogs with CKD, approximately one third will be normotensive, one third will have borderline hypertension, and one third will be hypertensive.

Systemic hypertension may contribute to progressive nephron loss by causing irreversible glomerular damage via increased intraglomerular pressures and glomerulosclerosis. By altering pre-glomerular resistance, healthy kidneys can maintain relatively static glomerular capillary pressures despite variations in systemic blood pressure. This process is termed *renal autoregulation*. Inappropriate dilation of the afferent glomerular arteriole occurs in dogs and cats with CKD and diminishes the ability of the afferent arteriole to protect the glomerulus from variations in systemic blood pressure. Although the exact mechanism of the renal-induced hypertension is not known, a combination of glomerular capillary and arteriolar scarring, decreased production of renal vasodilatory prostaglandins, increased responsiveness to normal pressor mechanisms, and activation of the renin-angiotensin system secondary to impaired sodium excretion and excessive renin secretion may be involved. The increased renin secretion leads to increased production of angiotensin II and aldosterone. In addition to its pressor effects, angiotensin II also has a direct stimulatory effect on the sympathetic nervous system, increasing vascular tone, and, in CKD vasoconstriction of the efferent arteriole, which further contributes to the intraglomerular hypertension.

The consequences of hypertension are usually dependent on the magnitude and duration of the blood pressure elevations. Acute ocular and central nervous system abnormalities can occur associated with hemorrhage or edema formation (eg, retinal hemorrhage and/or detachment and cerebral edema). Renal damage associated with hypertension tends to be more chronic and characterized by glomerular lesions (eg, glomerulosclerosis) and proteinuria. Finally, functional/adaptive changes like ventricular hypertrophy can occur due to increased after-load in patients with hypertension. Diagnosis and treatment of hypertension in dogs and cats with CKD renal may prevent development of retinal lesions or may limit or slow progression of renal and cardiac lesions.

PROTEINURIA

Renal proteinuria is both a diagnostic marker of the severity of renal disease and a mediator of glomerular and tubular injury. Excessive protein in the glomerular filtrate can cause glomerular lesions as well as tubulointerstitial lesions leading to loss of more nephrons. Recent findings have demonstrated that proteinuria is associated with increased risk of developing end-stage CKD in dogs and cats. In addition, studies have shown that therapies that reduce the magnitude of proteinuria are often renoprotective. Proteinuric renal disease is often associated with systemic hypertension, which can conversely exacerbate renal proteinuria and therefore, it is difficult at times to separate the effects of high systemic and intraglomerular pressures and proteinuria.

DIAGNOSIS OF HYPERTENSION AND PROTEINURIA

Current recommendations are that blood pressure be measured in a quiet area prior to examining the patient, typically in the presence of the owner and after a 5- to 10-minute period of acclimation. The ACVIM Panel on Hypertension suggests discarding the first measurement, then obtaining a minimum of 3, preferably 5 to 7, consecutive measurements with less than 20% variability in systolic blood pressure. Conditions (including animal's disposition), cuff size, measurement site and all measured values should be recorded in the medical record. Many clinicians require that hypertension be documented on more than one occasion before accepting the diagnosis.

Diagnosis and management of proteinuria in cats and dogs with CKD should be accomplished in a step-wise fashion. The specificity of the dipstick-screening test for proteinuria is poor and therefore confirmation of proteinuria should be accomplished with a more specific follow-up test such as the sulfosalicylic acid (SSA) turbidimetric test, UP/C, or species-specific albuminuria assay. The second step is assessment of proteinuria is to determine its origin. Proteinuria of renal origin can adversely affect the prognosis of dogs and cats with CKD and therefore, physiologic or benign proteinuria and pre- and post-renal proteinuria should be ruled out. Subsequently, via serial monitoring, it should be determined if the proteinuria is persistent or transient. Persistent proteinuria is defined as at least two positive tests at two-week intervals. Relatively mild proteinuria in dogs and cats with spontaneous/naturally-occurring CKD appears to be a negative predictor of survival. In dogs and cats with the remnant kidney model of CKD, proteinuria is associated with nephron hypertrophy and increased intraglomerular pressures. Persistent proteinuria of renal origin of a magnitude ≥ UP/C of 0.4 in cats and ≥ 0.5 in dogs with CKD should be treated with an ACEI and/or dietary protein reduction.

MANAGEMENT

Gradual reduction of dietary salt is often recommended as the first line of treatment for hypertension; however, there are no studies that document the efficacy of this treatment. In many cases, vasodilators (angiotensin-converting enzyme inhibitors [ACEI] and calcium channel antagonists [CCA]) may be necessary to control systemic hypertension. The CCA amlodipine is often recommended as the first choice antihypertensive treatment for cats; however, recent information has raised concerns that treatment with a CCA alone may activate the renin-angiotensin-aldosterone system and potentially create higher intraglomerular pressures via further efferent arteriolar vasoconstriction. Initial treatment with an ACEI may be appropriate in both dogs and cats with CKD because of the beneficial effects on intraglomerular pressure and proteinuria. In those cases where systemic hypertension persists after initiation of ACEI treatment, a CCA can be added. The overall risk of target organ damage to the eyes, brain, heart, and kidneys is thought to be minimal if systolic blood pressure is maintained at ≤ 150 mmHg.

WHAT EVIDENCE EXISTS THAT SYSTEMIC HYPERTENSION AND/OR PROTEINURIA ARE DETRIMENTAL TO CANINE AND FELINE KIDNEYS?

1. In dogs with the page/remnant kidney model of chronic renal failure (CRF), systemic hypertension had adverse effects on renal function and morphology. (Finco, JVIM 17:407, 2003)
2. In dogs with remnant kidneys, 40–45 mmHg increases in systolic blood pressure over baseline resulted in enhanced renal damage. (Brown, JVIM 14:351, 2000)
3. In dogs with spontaneous chronic renal failure, initial high systolic blood pressure was associated with increased risk of developing a uremic crisis and of dying. (Jacob, JAVMA 222:322-329, 2003)
4. Angiotensin-converting enzyme inhibition (ACEI) treatment that lowered systolic blood pressure was associated with improve outcome in dogs with spontaneous glomerulonephritis. (Grauer, JVIM 14:526-533, 2000)
5. ACEI treatment in dogs with remnant kidney CRF was effective in modulating progressive renal injury, which was associated with a reduction in glomerular and systemic hypertension. (Brown, AJVR 64:321-327, 2003)
6. Glomerular capillary hypertension, glomerular enlargement, and proteinuria have been documented in dogs with the remnant kidney model of renal failure. (Brown, Am J Physiol 258:F495-F503, 1990)
7. In cats with the remnant kidney model of CKD, increases in single nephron GFR occur in association with glomerular hypertrophy, increasing intraglomerular pressures, hyperfiltration, mesangial matrix expansion, and proteinuria. (Brown, Am L Physiol 269:R1002-R1008, 1995)
8. In dogs with naturally occurring CKD, the relative risk of uremic crises and mortality was approximately three time greater in dogs with UP/Cs > 1.0 (n=25) compared with dogs with UP/Cs < 1.0 (n=20). In this study, the risk of an adverse outcome was approximately 1.5 times greater for every 1-unit increase in UP/C and the decline in renal function was greater in dogs with higher UP/Cs. (Jacob, AJVR 226:393-400, 2005)
9. In cats with naturally occurring CKD, relatively mild proteinuria (UP/Cs > 0.4) appear to be negative predictors of survival. Increasing proteinuria was associated with increasing serum creatinine concentrations and increasing systolic blood pressure (presumably related to glomerular hyperfiltration). UP/C, age, and serum creatinine concentration (but not blood pressure) were independently associated with mortality. (Syme, JVIM 20:528-535, 2006)
10. In 141 client-owned cats with hypertension that were treated with amlodipine, proteinuria (as measured by the UP/C) decreased. Proteinuria before and after treatment of hypertension was strongly associated with survival but systolic blood pressure was not. (Jepson, JVIM 21:402-409, 2007)
11. In 61 cats with naturally occurring chronic kidney disease, treatment with benazepril decreased proteinuria (UP/C) compared with placebo treatment. Incidence rates of cats with stage II or III CKD that remained in stage II or III without progressing to stage IV were higher in the benazepril treatment group compared with the placebo treatment group. (Mizutani, JVIM 20:1074-1079, 2006)
12. In 13 cats with naturally occurring CKD and higher magnitude proteinuria (UP/C > 1.0), survival time was increased in those cats treated with benazepril compared with those cats treated with placebo (402 vs. 149 days). (King, JVIM 20:1054-1064, 2006)
13. Proteinuria has been associated with increased risk of mortality due to all causes in cats that have normal renal function when their proteinuria is first detected. (Walker, JVIM 18:417, 2004)

HOW I TREAT CALCIUM OXALATE UROLITHS

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To prevent recurrent calcium oxalate (CaOx) uroliths therapy should be designed to decrease urine concentrations of lithogenic minerals and to increase urine concentrations of stone inhibitors. This can be accomplished through a variety of dietary and pharmacologic interventions.

CLIENT COMPLIANCE

We have found that veterinarians and their staff typically overestimate the degree to which clients comply with treatment and management recommendations. To achieve reasonable compliance, the veterinarian must include clients in planning the preventative protocol so that clients will understand what they can and will do and what is essential to maintain the animal-human bond. For example, therapy requiring changes in lifestyle (meal feeding versus ad libitum feeding), difficult tasks, confusion about instructions, too many instructions, and frequent changes in instructions may lead to premature discontinuation or mistakes in therapy.

Table 1. Some Human Foods Permissible to Feed to Dogs and cats with Calcium Oxalate Urolithiasis*

Meats	Eggs Poultry
Vegetables	Avocado Cabbage Cauliflower Mushrooms Peas, green Radishes White potatoes
Fruits	Avocado Banana Bing Cherries Grapefruit Green grapes Mangos Melons: cantaloupe, casaba, honeydew, watermelon Plums: green or yellow
Breads, grains, nuts	Macaroni Rice Spaghetti
Miscellaneous	Popcorn Jellies Preserves

*These foods have minimal calcium and oxalate content

Scheduled re-exams are likely to motivate the client to comply with long-term preventative therapy. Also by educating the client about the purpose of therapy, and the expected outcomes, clients are more likely to be motivated to achieve these goals.

How can compliance be verified? Decreased urine specific gravity and less acidic urine are usually associated with diet compliance. An expectation of full compliance may be unrealistic. In general, less than full compliance is acceptable to us, as long as the desired therapeutic benefit can be safely achieved. Once a preventative protocol is agreed upon, follow-up evaluation is important.

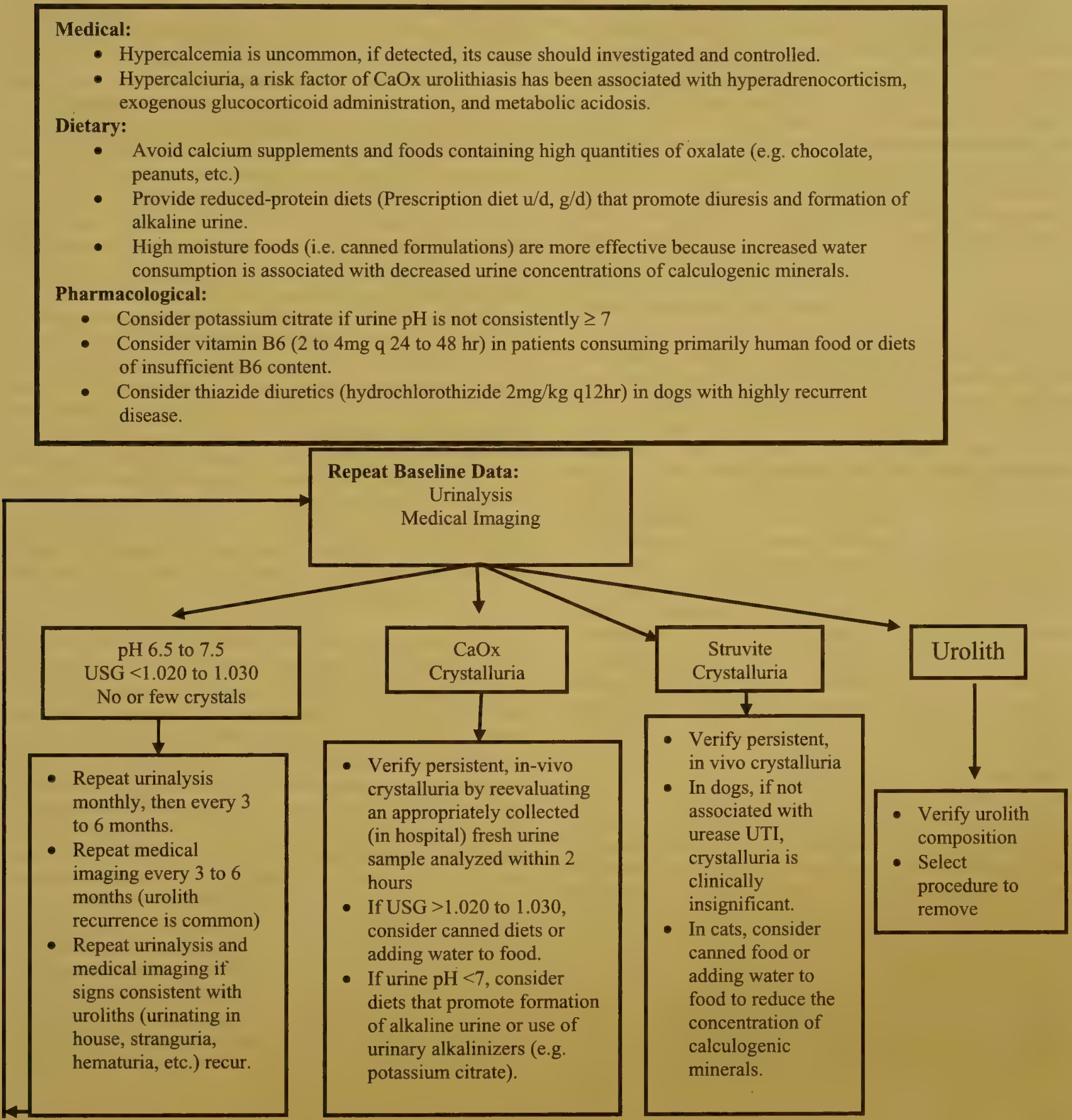
Table 2. Some Human Foods To Avoid Feeding to Dogs and Cats with Calcium Oxalate Urolithiasis

Meats	Bologna Herring Oysters Salmon Sardines
Vegetables	Asparagus Baked beans Broccoli Carrots Celery Corn Cucumber Eggplant Green beans Green peppers Lettuce Spinach Sweet potatoes Tofu Tomatoes
Milk and Dairy Products	Cheese Ice cream Milk Yogurt
Fruits	Apples Apricots Cherries Most berries Peel of lemon, lime or orange Pineapple Tangerine
Breads, grains, nuts	Corn bread Fruit cake Grits Peanuts Pecans Soybean Wheat germ
Miscellaneous	Beer,Chocolate,Cocoa,Tea

KEY POINTS

1. The most plausible explanation for recurrence of calcium oxalate uroliths within days to weeks following cystotomy is incomplete surgical removal of all uroliths during the previous surgery.
2. Recurrence of small uroliths in the urinary bladder can be removed non-surgically by voiding urohydropropulsion.
3. Most clients lack the training and experience to appropriately collect urine at home. Don't waste time relying on these inappropriate samples for making accurate medical decisions.
4. Dogs at risk for both struvite and calcium oxalate uroliths can be successfully managed by modifying the diet to minimize calcium oxalate and by controlling urinary tract infection to minimize struvite.

Figure 1. Algorithm for Management of Calcium Oxalate Uroliths in Dogs and Cats



Medical:
- Hypercalcemia is uncommon, if detected, its cause should investigated and controlled.
- Hypercalciuria, a risk factor of CaOx urolithiasis has been associated with hyperadrenocorticism, exogenous glucocorticoid administration, and metabolic acidosis.

Dietary:
- Avoid calcium supplements and foods containing high quantities of oxalate (e.g. chocolate, peanuts, etc.)
- Provide reduced-protein diets (Prescription diet u/d, g/d) that promote diuresis and formation of alkaline urine.
- High moisture foods (i.e. canned formulations) are more effective because increased water consumption is associated with decreased urine concentrations of calculogenic minerals.

Pharmacological:
- Consider potassium citrate if urine pH is not consistently ≥ 7
- Consider vitamin B6 (2 to 4mg q 24 to 48 hr) in patients consuming primarily human food or diets of insufficient B6 content.
- Consider thiazide diuretics (hydrochlorothizide 2mg/kg q12hr) in dogs with highly recurrent disease.

Repeat Baseline Data:
Urinalysis
Medical Imaging

pH 6.5 to 7.5
USG <1.020 to 1.030
No or few crystals

- Repeat urinalysis monthly, then every 3 to 6 months.
- Repeat medical imaging every 3 to 6 months (urolith recurrence is common)
- Repeat urinalysis and medical imaging if signs consistent with uroliths (urinating in house, stranguria, hematuria, etc.) recur.

CaOx
Crystalluria

- Verify persistent, in-vivo crystalluria by reevaluating an appropriately collected (in hospital) fresh urine sample analyzed within 2 hours
- If USG >1.020 to 1.030, consider canned diets or adding water to food.
- If urine pH <7, consider diets that promote formation of alkaline urine or use of urinary alkalinizers (e.g. potassium citrate).

Struvite
Crystalluria

- Verify persistent, in vivo crystalluria
- In dogs, if not associated with urease UTI, crystalluria is clinically insignificant.
- In cats, consider canned food or adding water to food to reduce the concentration of calculogenic minerals.

Urolith

- Verify urolith composition
- Select procedure to remove

Table 3. Common Medications Used in the Management of Calcium Oxalate Uuroliths

Drug Name	**Brand Name(s)**	**Dosage**	**Comments**
Potassium citrate	Urocit -K (Mission Pharmacal) Polycitra-K (Willen Pharmaceuticals) Vet Life (Lander Corporation)	40 to 75 mg/kg q 12 hour	5 meq = 540 mg adjust dosage to maintain a urine pH between 6.5 and 7.5
Hydrochlorothiazide	HydroDiuril (Merck)	2 to 4 mg/kg q 12 hour	Contraindicated if hypercalcemic. Use cautiously in cats
Pyridoxine HCl	Vitamin B6	2 mg/kg daily	
Phosphate	Neutra-Phos-K (Willen Pharmaceuticals) Neutra-Phos (Willen Pharmaceuticals)	250mg/day ?	Adjust dosage to maintain serum phosphorus concentration within the normal range

UROLITHIASIS: FROM HIPPOCRATES TO STAR WARS

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Hippocrates, a Greek physician born in 460 BC, was regarded as the greatest physician of his time. He based his medical practice on observations and on the study of the human body. He held the belief that illness had a physical and a rational explanation. He rejected the views of his time that considered illness to be caused by superstitions and by possession of evil spirits and disfavor of the gods. He was also the first physician that held the belief that thoughts, ideas, and feelings come from the brain and not the heart as others of his time believed. Hippocrates founded a medical school on the island of Cos, Greece and began teaching his ideas. He soon developed an Oath of Medical Ethics for physicians to follow. This Oath (although modified) is upheld by physicians today as they begin their medical practice. Prominently displayed in the original oath was the following quote… I will not cut for stone." The oath prohibited physicians from performing cystotomy to remove stones because this oath outlined the duties of healers and prohibited doctors from harming. Using the knife to manage stones was prohibited because in the time of Hippocrates it was associated with many complications; severe fever, urine fistula, septicemia, and reduced sexual potency. Therefore, stone removal was left to the practice of itinerate rouges (carnival medicine men). Although, today for reasons that are quite different, his warning to avoid the knife in the treatment of stones to minimize patient suffering is becoming a reality for companion animals. It is our belief that one day soon non-surgical procedures will become the standard of care for the veterinary profession.

MAKING EFFECTIVE AND ETHICAL CHOICES

The need for urolith removal and selection of operation depends on the effects of the urolith on the patient (asymptomatic, recurrent infection, dysuria, and urinary obstruction), the characteristics of the urolith (mineral composition, size, contour, number, and location), and veterinarian preferences and experience (availability of special equipment and familiarity with procedures). Our goal for urolith removal is to provide a safe and effective procedure with minimal risk and maximal comfort. In addition to urolith removal, the process should be associated with a quick recover and rapid return to normal function. Newer diets, minimally invasive procedures, and advanced technologies afford most patients with uroliths a safe and minimally invasive process without irreversibly altering their normal anatomy. For example, the availability of laser lithotripsy precludes the need to perform prescrotal urethrostomy surgeries for correction of urethrolithiasis.

Medical Dissolution

Medical therapy to dissolve calcium oxalate (CaOx) uroliths has yet to be developed. However, uroliths composed of magnesium ammonium phosphate (struvite) can be dissolved medically with a high degree of success.[1] Typically, sterile struvite uroliths dissolve in 2 to 4 weeks with diets that provide reduced quantities of magnesium and phosphate, and promote formation of acidic urine. When formation of struvite stones results from urinary tract infection caused by urea-splitting bacteria, dissolution time is typically longer (2 to 3 months). When managing infection-induced struvite uroliths, remember that in addition to urolith-dissolution diet, appropriate antimicrobics are necessary throughout the entire period of dissolution. It is important to recognize that uroliths located in the urethra and upper urinary tract are less likely to dissolve because they are not continually surrounded by urine that is undersaturated for magnesium ammonium phosphate. Therefore, urethroliths need to be flushed back into the urinary bladder and their position periodically monitored to improve success of dissolution therapy. In addition to uroliths composed of magnesium ammonium phosphate, uroliths composed of salts of uric acid, cystine, and xanthine are also amenable to medical dissolution.

Voiding Urohydropropulsion

Until recently, most uroliths in the urinary bladder were either medically dissolved or surgically removed. However, at the University of Minnesota, we developed a new technique to remove urocystoliths, called *voiding urohydropropulsion*. By taking advantage of the effect of gravity on urolith position in the urinary bladder and dilation of the urethral lumen during the voiding phase of micturition, this simple technique allows uroliths to be rapidly flushed out of the urinary tract.

Over the past 10 years, voiding urohydropropulsion has been used to remove uroliths in over 1000 dogs at our hospital. We have found voiding urohydropropulsion to be an effective and safe method to remove small to moderately sized urocystoliths of any mineral composition. Many are afraid to use this technique to remove stones for fear of urethral obstruction resulting from stones becoming irrevocably lodged in the urethral requiring a urethrotomy. This is not true; stones that become lodged in the urethra during voiding urohydropropulsion are quickly and easily flushed back into the urinary bladder. Some are afraid that they will rupture the urinary bladder during voiding urohydropropuslion. To avoid this potential complication, insure that the patient is anesthetized sufficiently to relax the urethral sphincters (this level of anesthesia is often greater than what routinely sufficient for a celiotomy), and never perform this technique on patients who recently had a urethral obstruction or bladder surgery.

To ensure success with this technique, your first patient should be approximately 7 to 11 kg in body weight. When choosing a female dog, uroliths should not be larger than 5 mm in diameter; in a male, uroliths should not be larger than 3 mm in diameter. With experience and practice, successful removal of larger stones is easily accomplished.

Basket Retrieval

Retrieving stones cystoscopically with a stone basket is ideal for removing small stones that can be easily pulled through the urethra. This simple procedure requires general anesthesia. Approximate procedure time depends on the number of stones in the urinary bladder, but most are completely removed in 5 to 15 minutes. A variety of stone baskets are available to facilitate removal (Stone Retrieval Grasping Forceps, Boston Scientific; MA; N-Circle® Nitinol Tipless Stone Extractor, Cook Urologic; Bard Dimension Stone basket, C.R. Bard).

Intracorporeal Laser Lithotripsy

Use of laser energy for intracorporeal lithotripsy is a relatively new concept. In 1968, investigators first reported in vitro fragmentation of uroliths with a ruby laser. However, because fragmentation of stones was associated with generation of sufficient heat that would likely damage adjacent tissues, it could not be used to treat patients. Likewise, use of carbon dioxide laser energy was considered to be unsuitable for clinical use because it could not be delivered through nontoxic fibers. However, in 1986 researchers using a 504-nm, pulsed dye laser successfully and safely treated human patients with ureteroliths. The holmium:YAG laser is the newest device available for clinical lithotripsy.

The mechanism of stone fragmentation with the Holmium:YAG laser is mainly photothermal, and involves a thermal drilling process rather than a shock-wave effect. Ho:YAG laser energy is transmitted from the crystal to the urolith via a flexible quartz fiber. To achieve optimum results, the quartz fiber tip must be guided with the aid of a cystoscope so that it is in direct contact with the surface of the urolith.

Holmium:YAG laser technology is capable of fragmenting all types of biogenic stones. Stones lodged in the male urethra of dogs are the easiest to manage typically requiring only 3 to 7 minutes to fragment and remove. However, this minimally invasive procedure usually takes about 10 to 20 minutes longer than surgical removal via cystotomy, and correlates with the volume of stones in the urinary bladder. Because urinary tract instrumentation with cystoscopy equipment is needed to perform lithotripsy, the narrow lumen of the feline urethra limits the feasibility of laser lithotripsy in the male cat.

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Table 1. Methods of Urolith Removal

	Method	Suitable Application	Considerations
Least Invasive	Spontaneous voiding	Small (< 3 to 5 mm), asymptomatic urocystoliths with a relatively slow growth rate (ie, calcium oxalate, calcium phosphate, uric acid) in female patients	Patients with uroliths larger than the urethral lumen may develop urethral obstruction Concomitant UTI should be eradicated
	Medical Dissolution	Sterile struvite, infection-induced struvite, allopurinol-induced xanthine, uric acid, and cystine stones are amenable to medication dissolution. See our website: http://www.cvm.umn.edu/depts/minnesotaurolithcenter/home.html	Sterile struvite and allopurinol-induced xanthine uroliths dissolve within weeks Large infection induced struvite stones may take 2 to 3 months to dissolve Stones in kidney require longer dissolution times than stones in the bladder Urethral obstruction is uncommon during dissolution unless the dog is a very dysuric male.
	Catheter retrieval	To retrieve small urocystoliths (<3 mm) for quantitative mineral analysis	Can be performed without anesthesia

Most Invasive	Voiding Urohydropropulsion	To evacuate small to moderate size (<5 to 7 mm) urocystoliths of any composition	Not suitable for male cats unless they have a perineal urethrostomy Not suitable for patients with a urethral obstruction Not ideal for patients that have recently undergone bladder surgery Eradicate urinary infection prior to performing VUH
	Stone Basket Retrieval	Urocystoliths smaller than (<5 to 7 mm) the urethra	Performed during cystoscopy. Stone retrieval baskets are delicate and break easily.
	Urolith Evacuators	Small urocystoliths or urolith fragments following lithotripsy in large female dogs	Most evacuators are designed to fit only the sheath of human cystoscopes (17Fr (5.6mm)) Best suited to remove uroliths and urolith fragments in large dogs too heavy voiding urohydropropulsion
	Intracorporeal Lithotripsy (laser, ultrasonic, or ballistic)	Urocystoliths in female dogs and cats and urethroliths in male dogs.	Performed during cystoscopy The flexibility of probes for laser lithotripsy permit fragmentation of urocystoliths in male dogs The urethra of the male cat will rarely accommodate cystoscopy equipment to perform lithotripsy Large hard uroliths (calcium oxalate monohydrate) in male dogs requires longer times to fragment. Placing uroliths in the urethra (basketing) facilitates lithotripsy. Ideal for uroliths lodged in the urethra.
	Extracorporeal shock wave lithotripsy (ESWL)	Ureteroliths and nephroliths in dogs	Uroliths in the renal pelvis are easier to fragment than ureteroliths The ability to perform ESWL without damaging feline kidneys is controversial-newer generation lithotripters may prove safer
	Laproscopic assisted cystotomy	Urocystoliths in dogs	Requires training in cystoscopy and laproscopic surgery
	Cystotomy/ Urethrotomy/ urethrostomy	Urocystoliths or uroliths lodged in the urethra	Consider retrograde urohydropropulsion of urethroliths prior to urethral surgery Cystotomy- failure to remove all uroliths in 15-20% of cases
	Ureterotomy/ Ureteroneocystotomy/ Ureteroneoureterotomy	Clinically active ureteroliths	High degree of surgical skill required when performed on cats Surgery performed on dilated ureters has been associated with greater success than normal sized ureters
	Pyelotomy/ nephrotomy	Nephroliths or ureteroliths flushed into the kidney	Some reduction in kidney function should be anticipated following surgery Difficult to locate some stones in renal pelvis

ECTOPIC URETERS AND URINARY INCONTINENCE: SELECTING THE RIGHT TEATMENT FOR EACH PATIENT

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In juvenile dogs and cats anatomic defects resulting from disturbed localized embryogenesis are the most common cause of urinary incontinence. The subsequent dysfunction of either the urethra or ureter usually leads to more or less continuous urine dribbling and sometimes urine scalding of the skin in the genital area. Some of these congenital problems occur combined with purely functional disorders responding to conservative treatment but generally can only be corrected by surgical treatment in the long term. We have identified prognostic factors in dogs with ectopic ureters which may be very helpful in making a decision which kind of treatment is the most appropriate for each patient.

The inappropriate termination of one or both ureters is the most common cause of urinary incontinence in juvenile dogs. It occurs much less frequently in male dogs than in female dogs and is extremely rare in cats. In dogs, breeds such as Labrador and Golden Retrievers and Siberian Huskies are overrepresented. During embryogenesis the ureters develop from the metanephric duct and terminate in the urogenital sinus. During differentiation of the urogenital sinus into the bladder and urethra, the termination may grow into the caudal direction with the result that the ureter does not open into the trigonal area of the bladder but will develop as an intramural tubular structure parallel to the urethra. From outside the bladder the situation might therefore look normal, while the urine is transported right into the urethra or vagina. Depending on the location of the opening where the urine enters the urethra, urinary incontinence is caused solely by passing by the sphincter mechanism or by a combination of an ectopic termination and urethral sphincter mechanism incompetence (USMI). The latter type of patient will not respond to surgical correction of the ureter alone but requires treatment of the USMI.

The diagnosis of ectopic ureters may be made by intravenous urography (x-ray or computed tomography [CT]), retrograde contrast radiography of the urethra and bladder, by ultrasonography of the kidneys, ureter and bladder or by endoscopy. Endoscopy is the best method to determine the precise termination of the ureter, while sonography is the most practical method to determine dilation of the ureter and estimate the degree of hydroureter and hydronephrosis. Hydronephrosis may develop through the resistance of the ureter when it has to pass the sphincter mechanism. In a study of 48 dogs with ectopic ureters, we identified diagnostic parameters indicating the presence of USMI that can be applied in a clinical situation without need for urodynamic investigations, which are difficult to apply due to technical problems in dogs with ectopic ureters anyway.

First, from the clinical history, dogs with concurrent USMI often leak only intermittently, that is, when in recumbency. Second, in female dogs there is evidence of dilatation of the ureter and/or the renal pelvis, indicating some outflow obstruction. The termination of the ureter determines whether this is happening and there is high correlation between a termination distal to the proximal urethra and ureteral dilatation. An exception would be a so-called ureterocoele with a thin membrane occluding the ureteral orifice. However, this is easily identified with sonography of the bladder neck. Third, there often is evidence of a so-called pelvic bladder, an unusual caudal position of the bladder. This has been found to be a sensitive indicator of USMI in female dogs in general. Last, but not least, there is response to medical therapy. If phenylpropanolamine is administered, dogs with USMI very often respond to the treatment and signs of urine dribbling disappear or at least improve. These four factors should be considered before a decision is made to repair ectopic ureters surgically once the finding of an abnormal termination of the ureters is made with diagnostic imaging.

The author currently selects patients for surgery of the ureter by the following criteria:

- Continuous dribbling of urine
- Dilation of the ureter and/or renal pelvis or termination caudal to the proximal urethra
- No evidence of a pelvic bladder
- No response to administration of phenylpropanolamine (PPA)

If concurrent USMI has been identified, a decision for surgery is postoponed and dogs are treated with PPA until the first heat. If USMI is not managed successfully and/or does not disappear with the influence of endogenous estrogen during the first heat, a surgical management of USMI by colposuspension or urethral sling procedure is considered.

If the criteria mentioned above are fulfilled there are two relevant techniques to surgically correct ectopic ureters in dogs without USMI. Although nephrectomy may be an option, this should be the last resort. For most female dogs, a technique called *ureterneostomy* would be recommended, while in male dogs and cats a so-called *ureteral reimplantation* is the appropriate procedure. In general, animals should be treated with antimicrobial agents prior to surgery because of the high incidence of urinary tract infection.

URETERNEOSTOMY

The animal is in dorsal recumbency. The abdomen is entered by a caudal midline incision. The ventral ligament of the blader is severed. The bladder is lifted out and pulled forward using stay sutures in the bladder wall. The bladder neck area is incised to expose the trigonal area. The intramural location of the ureter is palpated and the mucosa is then incised above the ureter. The ureter can then be grasped with delicate forceps and a stay suture using 6-0 suture material is placed through it. The ureter is then carefully dissected from the surrounding tissue and the distal, ectopic part is ligated with 4-0 USP multifilament absorbable suture material. The ureter is then transsected and the opening is sutured to the mucosa of the bladder using 6-0 multifilament absorbable suture material. Four to eight single interrupted sutures are usually necessary to adapt the lumen of the ureter to the incicion in the mucosa of the bladder. The bladder incision and abdominal wound are then closed routinely.

Intraoperative complications are bleeding from the submucosa and edema, interfering with proper suturing. Postoperatively stricture formation is quite rare with this technique, but recanalization may occur, and depending on the size of the ureter, reflux from the bladder into the ureter.

URETERAL REIMPLANTATION

This technique tries to create a new physiological termination; therefore, a submucosal tunnel is created to prevent reflux. The bladder is reflected caudally to expose the trigonal area and to locate the ureter. It is then dissected from the lateral ligament of the bladder and ligated closed to the bladder. After transsection a stay suture using 6-0 suture material is placed through the wall of the ureter. Small stab incicions are then made in the serosa and muscular layer of the dorsal bladder wall. Hemostatic forceps are used to create an tunnel in the submucosa. The bladder is then reflected and pulled in a cranial direction and opened by incising the ventral side. The tips of the forceps are located and stab incicions are made to peforate the mucosa. The stay suture of the ureter is then pulled throught the tunnel and the opening of the transsected ureter is sutured to the bladder mucosa as described above. The bladder and abdominal wound are closed routinely.

Intraoperative complications are also due to bleeding and swelling of the bladder mucosa and submucosa. With a bilateral procedure this might even cause ureteral obstruction postoperatively with severe consequences. Atraumatic tissue handling is therefore essential. The author recommends high diuresis fluid therapy starting immediately after surgery for 24 hours to keep the anastomosis flushed and open. Nevertheles leaking of urine from the anastomosis may occur and cause uroabdomen, peritonitis, and uremia. In the late postoperative period, stenosis of the anastomosis may occur and cause hydroureter and hydronephrosis. Therefore, postoperative controls using sonography are recommended in the first 2 to 6 weeks after surgery.

For the procedures to treat USMI surgically the interested reader is referred an article in last year's NAVC Proceedings.

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CASE STUDIES OF DOGS WITH PROSTATIC DISEASE: HOW FAR DO WE GET WITHOUT SURGERY?

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The following prostatic diseases can be managed by application of drugs and do not require surgical treatment:

- Benign prostatic hyperplasia (BPH)
- Acute infectious prostatitis
- Chronic prostatitis
- Prostatic neoplasia

MANAGEMENT OF BPH

The necessity to treat BPH depends on the severity of clinical signs. The majority of dogs have blood containing urethral discharge or tenesmus alvi. It is well recognized that castration will cause shrinkage of the prostate and these signs will disappear. However, any other way to reduce production and secretion of testosterone and estradiol by the testes will have the same result. This is achieved by administration of depot gestagens, which cause reduction of luteinizing hormone (LH) secretion from the pituitary gland and directly inhibit testosterone production in the Leydig cells of the testes.

The use of gestagens is well documented and it has been demonstrated that prostatic size is significantly smaller if measured by sonography 14 days after administration. The clinical signs may even disappear at an earlier stage. Most available gestagens such as delmadinon acetate, medroxyprogesterone, or megestrol acetate have a similar influence on prostatic tissue. However, the risk of developing insulin resistance or even manifest diabetes mellitus increases with the potency of the gestagen. Therefore, a weak gestagen such as delmadinon actetate is recommended. The injection of a depot preparation will usually keep the animal free of symptoms for approximately one year. Nevertheless, some cases do not improve after gestagen administration alone, but will improve after castration.

Gestagens, as with castration, may have an impact on behavior and other side effects that are not acceptable for the owner. For these cases the use of 5-alpha reductase inhibitors may be useful. These drugs, such as flutamid or finasteride, inhibit the conversion of testosterone into the active metabolite dihydrotestosterone (DHT) in the prostatic epithelial cells. By apoptosis in the stromal and glandular compartments of the prostate a decrease in the prostatic volume as much as 43% is achieved with daily administration of 0.5 mg/kg body weight. Fertility is not influenced by administration of the drug.

The use of estrogens is controversial because estrogens may cause bone marrow depression in dogs and also squamous metaplasia. The author does not recommend estrogens for the treatment of prostatic disorders in dogs.

INFECTIOUS PROSTATITIS

Although sensitivity testing is usually the basis of selecting an antibiotic for the treatment of a bacterial infection for the prostate there might be a difference. Some common antimicrobial agents doe not penetrate prostatic epithelial cells and fluid and might not reach the minimum inhibitory concentration. This depends on the lipid solubility of the drug and the pH difference between plasma and prostatic tissue. The recommended drugs to treat bacterial prostatitis are:

- Enrofloxacin (5–10 mg/kg/day)
- Marbofloxacin (2.5 mg/kg/day)
- Clindamycin (11 mg/kg/day)
- Chloramphenicol (50 mg/kg/8 hr)
- Trimethoprim/Sulfa (15 mg/kg/12 hr)

For the treatment of infection caused by some bacteria, such as *Pseudomonas* species, higher doses for a longer period may be necessary. In general a high risk of recurrence is present if the patient is treated for less than 4 weeks. In cases of chronic prostatitis, even longer periods of treatment have to be considered.

Adjunctive measures, such as castration or hormone treatment, may be necessary in chronic cases. In experimental studies castration alone was able to eliminate the inflammation. If castration is not an option antibiotic treatment alone can be tried. It may also be useful to search for defects in the local host defense mechanisms, since most infections are not limited to the prostate but a problem of the whole lower urinary tract.

PROSTATIC NEOPLASIA

Currently there is no treatment available to cure prostatic cancer or even cause long-term clinical remission. Still, the use of nonsteroidal anti-inflammatory drugs has shown to be a meaningful option in the management of prostatic cancer. This is due to their analgesic properties, but especially the inhibition of prostaglandin synthesis. In addition, elevated concentration of PGE_2 could be found in prostatic tumor tissue. Therefore, drugs selectively inhibiting this pathway, such as the cyclo-oxygenase-2 inhibitors, are real anti-tumor agents. It is the experience of the author that drugs such as piroxicam, meloxicam, and carprofen not only improve quality of life, but improve the clinical signs commonly observed in tumor patients. Depending on the severity of the disease the survival time might be up to a year or longer. In intact dogs, castration or additional hormone treatment may improve the clinical situation, but survival time has not been improved by these measures.

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PROSTATIC DISEASE: CASE DISCUSSION

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A case of prostatic disease is presented during this article, focusing on diagnostic techniques and their reliability. An overview of the diagnostic approach to prostatic disease in dogs is given here.

If prostatic disease is suspected to be the cause of clinical problems it may be difficult to make a diagnosis without more or less invasive procedures. The difficulty is to exclude severe conditions based on findings of the clinical history, physical examinations, blood and urine examinations, ultrasonography, and/or radiography. A safe way to come to a correct diagnosis is a diagnostic protocol including the following examinations and tests.

CLINICAL HISTORY

In order to suspect pathology of the prostate one or more of the following clinical signs must have been reported by the owner: tenesmus alvi, urethral/preputial discharge, dysuria, urinary incontinence, hematuria, abdominal or generalised pain, fever, anorexia, or hind leg lameness (Figure 1). If the animal was castrated long ago, neoplasia is much more likely.

PHYSICAL EXAMINATION

Fever, a palpable abdominal or perineal mass, painful reactions, and abnormal findings of a rectal examination may all further support a pathologic condition. If the prostate can be reached from the rectum with the finger, useful information might be obtained. Asymmetry is found often in the presence of cysts or abscess. Attachment, pain, and a firm consistency may be found with tumors.

LABORATORY FINDINGS

Most of the findings of hematologic examination and urinalysis are not very specific; still it may be helpful to detect a leukocytosis or pyuria. However, the absence of leukoctyosis or leukoctes in the urine does not exclude inflammation in the prostate. Microbiologic examinations can best be performed on semen specimens or prostatic fluids, which are especially useful in detection of prostatitis in infertile dogs and in selection of drugs based on sensitivity testing. In order to obtain prostatic fluid, a massage of the prostate is performed with a urinary catheter with its openings in the prostatic urethra. Tests for the presence of neoplasia, such as measurement of acidic phosphatase or prostate-specific antigen, have shown to be unspecific in dogs.

RADIOGRAPHY

Specific findings on survey radiographs, such as bone metastasis, air or calcifications in the parenchyma, or severe gross enlargement may indicate prostatic disease. More information may be gained by retrograde contrast radiographs, which may reveal reflux into prostatic structures and irregularities of the urethra indicating urethral carcinoma, and differentiate the bladder from the surrounding tissues. However, except for bone metastasis, which proves the presence of adenocarcinoma, a definitive diagnosis often can not be made.

ULTRASONOGRAPHY

Ultrasonography is probably the most useful diagnostic tool in order to identify prostatic parenchymal abnormality. It may be possible to make a difference between paraprostatic cysts, abscess, and parenchymal cysts. Neoplasia only sometimes develops a typical pattern of mixed echogenicity, but does not do so reliably. Without cystic lesions it is not possible to differentiate between inflammation, neoplasia, and BPH.

CYTOLOGY

Except for histologic examinations of material obtained by invasive procedures the most useful and reliable diagnostic tool is cytologic examination of biopsy specimens obtained by fine needle aspiration (FNAB) or catheter suction biopsy. The latter is more useful when tumors are suspected, but material obtained by FNAB may also be a reliable indicator of inflammatory processes.

Catheter suction biopsy is easily performed by applying a vacuum with a syringe on the openings of a urinary catheter placed in the prostatic urethra. The cells are flushed on a glass slide, dried, and stained with a quick hematologic staining method such as Diff-Quik or by the May-Grünewald-Giemsa technique. Fine needle aspirates are best obtained by parapreputial or perineal introduction of a long needle with a mandrin (such as a Menghini needle or spinal needle). The position of the needle can be directed under ultrasonographic guidance (Figure 2).

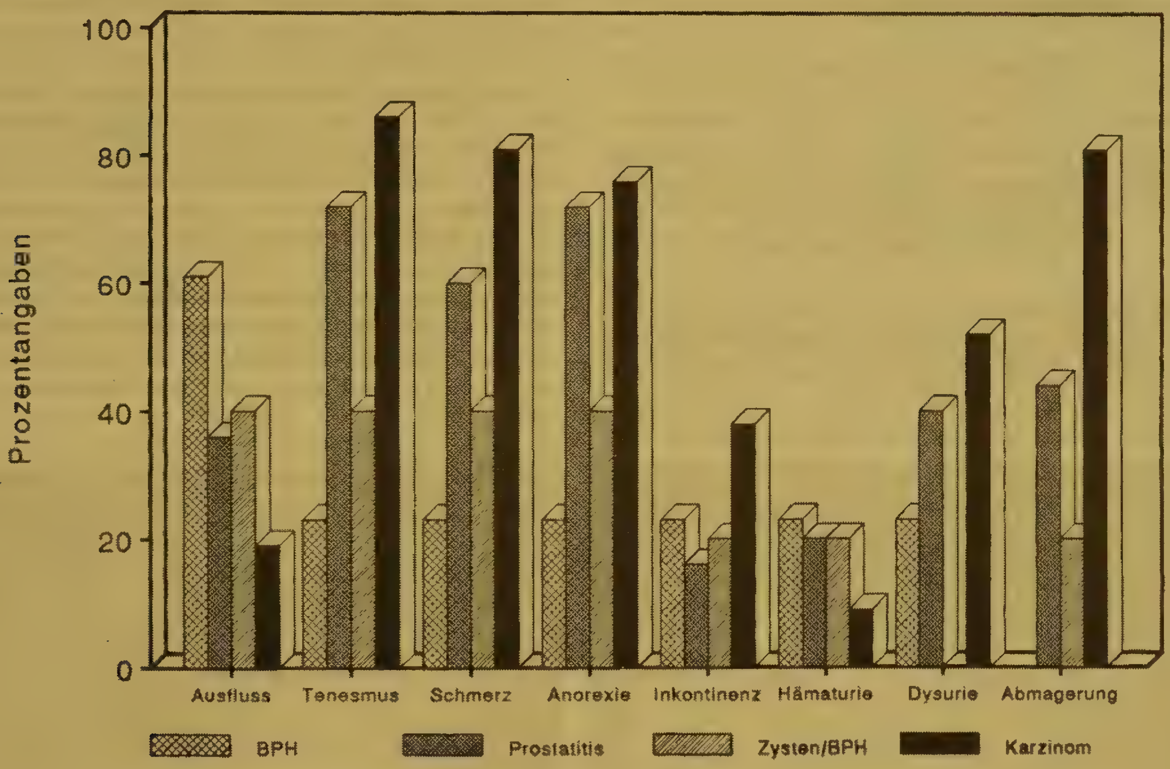

Figure. 1. Presentation of clinical signs in dogs with prostatic disease referred to the University of Utrecht (BPH = Benign prostatic hyperplasia; Zysten = cysts; Karzinom = carcinoma; Ausfluss = discharge; Schmerz = pain; Abmagerung = weight loss).

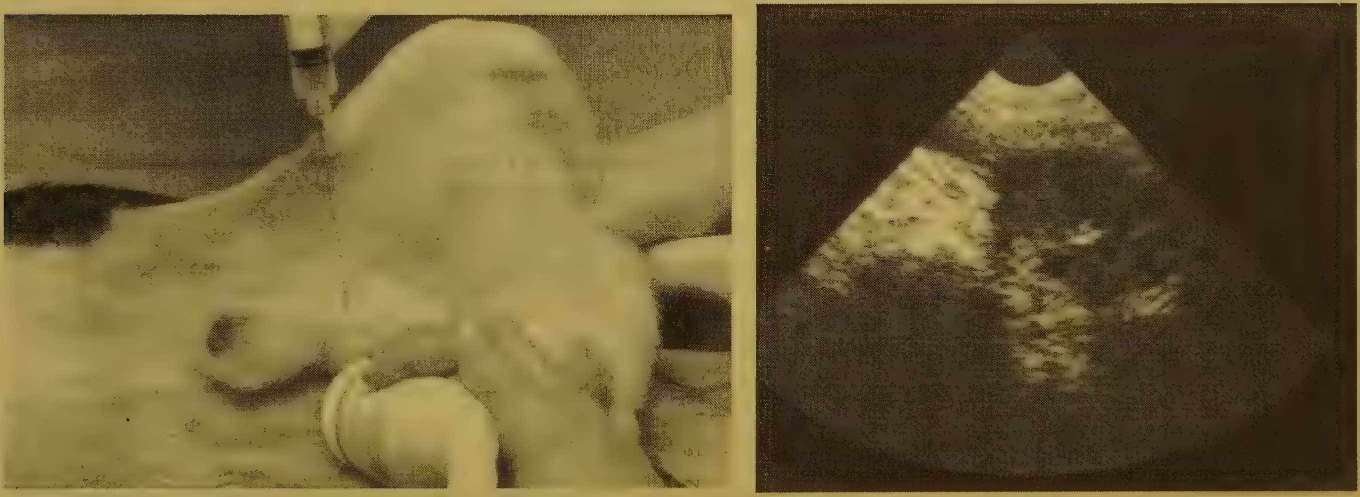

Figure 2. Positioning of the needle for aspiration of prostatic cells under ultrasonographic guidance in order to obtain material for cytologic evaluation

LASER-ASSISTED MINIMAL INVASIVE TREATMENT OF ECTOPIC URETERS

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As a supplement to the article "Ectopic Ureters and Urinary Incontinence: Selecting the Right Treatment for each Patient" by Dr. Nickel in this proceedings, we demonstrate the successful use of a diode laser for video-endoscopic surgical treatment in female dogs with intramural ectopic ureters.

Using a 30-watt diode laser with a 400-µm fiber (Limmer Laser, Germany) through the working channel of a 2.7-mm rigid endoscope (Karl Storz, Germany), we dissected the membrane between the urethra and the intramural ectopic ureter as far as proximal to the vesical sphincter.

The fascinating aspect of this new technique is the fact that diagnostic and curative intervention is performed simultaneously. We also demonstrate possible side effects in the form of accidental laceration of collateral urethral mucosa.

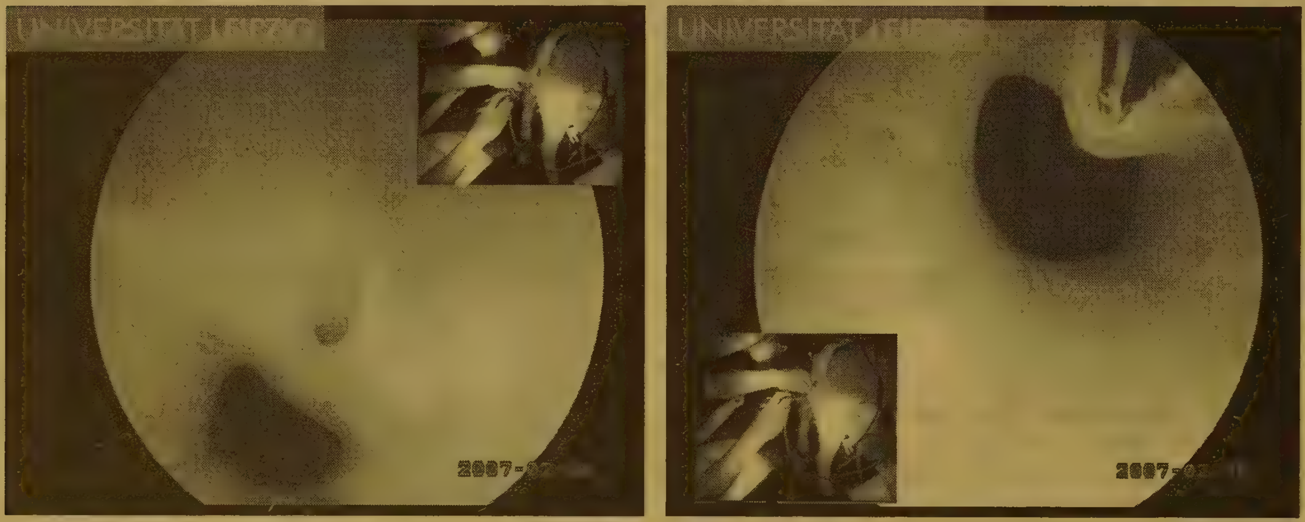

Figure 1. Distal opening of an intramural ectopic ureter (*left*) and dissection of the membrane between urethra and ureter with a diode laser fiber (*right*)

CHRONIC RENAL INSUFFICIENCY AND ASSOCIATED DISORDERS: KITTY KIDNEYS AND THE KITCHEN SINK

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Renal function declines with increasing age as a normal event. Consequently, renal insufficiency is very common in aging cats. The term *chronic renal insufficiency* is preferable to *chronic renal failure* because this condition is progressive, rather than imminently terminal, and can be treated. Cats may live for many years with decreased urine specific gravity and elevated blood urea nitrogen (BUN) and serum creatinine after the time of initial detection, depending on the disease's stage and cause. To grossly lump everything together as chronic renal failure is an over-simplification and disservice to our patients and clients. Recently, the International Renal Interest Society (IRIS) developed a four-level system for staging the continuum of progressive renal disease to use as a guide in diagnosis, prognosis, and treatment. Staging is based on the level of kidney function as determined by creatinine concentrations. Table 1 shows the criteria proposed by the IRIS in 2006 to characterize renal disease.

Staging allows for better communication between practitioners as well as offers guidelines for the initiation of different therapies. To provide high-quality patient care, practitioners must attempt to carefully define the stage of chronic renal disease, as well as identify and manage any concurrent medical conditions.

HISTORY

Clinical signs of renal insufficiency may include anorexia or inappetence, vomiting, dehydration, weight loss, lethargy, oral ulceration, ptyalism, anemia, social apathy, and constipation. Polyuria and polydipsia are reported less commonly than in dogs, perhaps because of the secretive nature of cats. In assessing the degree of illness, bear in mind that both decreased muscle mass (wasting) of cats with chronic renal insufficiency and concurrent hyperthyroidism will mask the severity of renal insufficiency by lowering serum creatinine levels. Often cats with even moderate renal insufficiency are

Table 1. Staging Chronic Renal Disease

Stage	**I** **Non-azotemic Renal Disease**	**II** **Mild Renal Azotemia**	**III** **Moderate Renal Azotemia**	**IV** **Severe Renal Azotemia or Chronic Renal Failure**
Creatinine: mg/dL (mmol/L)	< 1.6 mg/dL (< 140 mmol/L)	1.6 to 2.8 mg/dL (140 to 250 mmol/L)	2.8 to 5.0 mg/dL (251 to 440 mmol/L)	> 5.0 mg/dL (> 440 mmol/L)
Clinical signs	None	Possible inappetence, weight loss, polyuria, polydipsia	Usually inappetence, weight loss, polyuria, polydipsia	Uremia, clinically ill
Progression	Stable for long periods of time	Stable for long periods of time	May progress	Fragile
Therapeutic goals	Identify and treat specific primary kidney disease (*eg*, acute pyelonephritis, nephrolithiasis)	Identify and treat specific primary kidney disease (*eg*, acute pyelonephritis, nephrolithiasis)	Modify progression: phosphorus restriction, omega-3 fatty acids	Ameliorate uremic signs: protein restriction, antiemetics, erythropoietin, fluid therapy, appetite stimulation, dialysis
Proteinuria	Classify (see below)	Classify	Classify	Classify
Blood pressure	Classify (see below)	Classify	Classify	Classify

Proteinuria
Determined by evaluating sequential urine protein to creatinine (UPC) ratios.
Nonproteinuric = UPC < 0.25
Borderline proteinuria = UPC 0.25 to 0.5; reevaluate after two months
Proteinuria = UPC > 0.4

Classification of blood pressure
NH = nonhypertensive = < 150 mmHg with no complications
BP = borderline hypertensive = 150 to 160 mmHg with no complications
Hnc = hypertension no complications = consistent systolic blood pressure values of >160 mmHg
Hc = hypertension with extrarenal complications = signs + > 150 mmHg

asymptomatic. We don't need to give them new kidneys—we just need to correct and maintain physiologic parameters that will enable them to enjoy a good quality of life.

Because these patients are older cats, they may have more than one clinical condition. It is not uncommon to have a patient with chronic renal insufficiency that also suffers from pyelonephritis, cardiac disease, or hypertension associated with renal or thyroid disease. Constipation is extremely common in elderly cats. There may be concurrent inflammatory bowel or small airway disease, diabetes mellitus, neoplasia, or osteoarthritis. These co-morbid conditions may complicate our ability to untangle a diagnosis and balance treatments for a specific patient.

DIAGNOSTICS

Following a comprehensive physical examination and consultation (including a fundic examination and blood pressure determination), a minimum database for cats beyond middle age (> 8 years) consists of a complete blood count (CBC) with differential, serum biochemistries (including T4), and a complete urinalysis. Cats with renal insufficiency classically have a urine specific gravity of < 1.040 despite some degree of dehydration. Additionally, with progressive decline in function, BUN and creatinine will exceed normal reference values in the re-hydrated patient. As renal disease progresses, there will be varying changes in urinary protein, potassium levels as well as alterations in serum electrolytes (iCa, phosphorus, potassium). Anemia also develops due to several causes (discussed below).

Urinalysis should be collected by cystocentesis. Because pyelonephritis is often subclinical, urine culture and sensitivity testing should be considered in every patient with dilute urine (urine specific gravity < 1.020) and white blood cells or trace protein without adequate blood or red blood cells to account for the protein. The method of urine collection (free-catch vs. cystocentesis) affects the interpretation of bacterial colony counts. If the urine is collected by cystocentesis, any number of bacteria is significant. Collected by free catch, bacterial colony counts need to be > 10,000/mL to be significant.

Both dilute urine and glucosuria encourage bacterial growth. Serum fructosamine may be recommended depending on clinical concerns and diagnostic findings.

MANAGEMENT OF CHRONIC RENAL DISEASE

Hydration

In cats with chronic renal disease, rehydration is a key component of therapy. Rehydration is critical in tissue perfusion (oxygen and nutrients), scavenging waste and acid-base homeostasis. Because cats with renal insufficiency are usually in a state of metabolic acidosis, alkalinizing fluids are the preferred fluid type. In dehydrated patients, increased urea reabsorption due to decreased tubular flow rates may lead to an increase in BUN—even before the glomerular filtration rate is decreased—causing prerenal azotemia. This also causes serum BUN to appear greater than it actually is. Rehydrate the patient and repeat the blood work before giving a prognosis. With an impaired ability to concentrate urine, despite polydipsia, exogenous fluids are required. Clients commonly administer subcutaneous fluids to cats at home. Increasing oral intake of water can be encouraged through flavouring water, offering milk, and feeding more canned foods. Recirculating water fountains may appeal to some cats.

What about cats with a fragile cardiovascular system? Finding the balance between hydration maintenance to optimize renal function yet not overload cardiovascular capabilities requires fine-tuning through ongoing client communication. This requires frequent reassessment of packed cell volume (PCV), total solids, BUN, and serum creatinine, along with reassessment of body weight, skin elasticity, appetite, and energy.

For the most part, constipation is a clinical sign of dehydration. Cellular water content has priority over fecal water content; thus, primary treatment should address rehydration and the underlying cause of dehydration, rather than stool passage (eg, with laxatives). Promotility agents, laxatives, osmotic agents, and fiber-enriched diets should be used only after the patient is rehydrated.

Renally impaired cats with diarrhea from chronic small or large bowel disease have increased fluid losses above their maintenance replacement needs. Attempt to control the underlying cause of the diarrhea. Should corticosteroids be part of therapy (eg, inflammatory bowel disease or small airway disease), polyuria may worsen. Similarly, for cats with renal disease and diabetes mellitus, cellular water needs should be addressed.

Inappetence, Nausea, and Vomiting

Many cats with uremic gastritis show only signs of partial anorexia or nausea, rather than outright vomiting. H_2-receptor antagonists are underutilized; they function by preventing gastric hydrochloric acid production. Famotidine (0.5 mg/kg orally every 24 to 48 hours) or ranitidine (2 to 3 mg/kg orally every 12 hours) may be considered once serum creatinine is > 2.5 mg/dL (220 μmol/L), whether cats seem nauseated or not.

Appetite stimulation may be attempted with cyproheptadine (1 mg/cat orally every 12 hours) or mirtazapine (3 mg/cat orally every 72 hours), which has the added benefit of anti-emetic effects. Regardless of concurrent problems, adequate calories need to be ingested. For patients not ingesting adequate calories (weight loss, poor coat and muscle), placement of an esophagostomy or other large-bore feeding tube should be considered.

Hypertension

The incidence of hypertension in cats with renal insufficiency has been reported to be 60%, whereas in cats with hyperthyroidism, the incidence is between 40% and 60%. Evaluation of blood pressure should, therefore, be considered in all older cats and any ill cats. Cats with chronic renal insufficiency lose the normal autoregulatory capacity of the glomerular arterioles. This not only causes systemic hypertension but also promotes progression of renal insufficiency through glomerular injury.

Treatment of hypertension should be considered in cats with systolic blood pressure consistently greater than 180 mm Hg. Amlodipine is the most efficacious agent (0.625 mg/cat orally every 12 to 24 hours, increase gradually over weeks as needed), as it has a direct effect on the peripheral vasculature calcium channels. Angiotensin-converting enzyme (ACE) inhibitors are not as efficacious in decreasing systemic blood pressure. Beta-blockers reduce renin secretion and are similarly unimpressive for treating feline hypertension.

Metabolic Acidosis

Cats with chronic renal diseases commonly have metabolic acidosis. This acid-base imbalance promotes severe catabolism of endogenous proteins, exacerbates azotemia regardless of diet, promotes wasting (degradation of protein), inhibits protein synthesis, causes a negative nitrogen balance, and enhances hypokalemia. Acidosis should be aggressively corrected through the use of alkalinizing fluid therapy and H_2-receptor antagonist use.

ADDITIONAL TREATMENT OPTIONS FOR CHRONIC RENAL INSUFFICIENCY

ACE Inhibitors

A large, multi-institutional study (the BENRIC study[1]) assessed the effects of benazepril on chronic renal insufficiency in cats. Results of this and other smaller studies[2,3] showed no significant difference in survival time between benazepril or placebo administration. However, for cats with urinary protein loss (urine protein to creatinine ratio), benazepril treatment resulted in longer survival times and better appetite than placebo. Cats without protein-losing glomerulonephropathy may potentially be harmed by this agent because it diverts renal blood, causing a beneficially increased renal, interstitial blood flow but a potentially deleterious reduction in GFR. Before diagnosing a protein-losing glomerulonephropathy, sequential urine protein to creatinine ratios should be checked (two over a two-week period) to ensure that proteinuria is persistent, rather than physiologic and transient. Cats with an increased urine protein to creatinine ratio (> 0.4) that are started on benazepril (0.25–0.5 mg/kg PO once daily) should be rechecked within 3 to 7 days and have their renal parameters, hydration, body weight, appetite, and overall health monitored. Thereafter, re-evaluate stable patients every 2 to 4 months.

Erythropoietin

Erythropoietin causes rapid correction of anemia by stimulating marrow progenitor cells. When PCV is < 20%, consider using erythropoietin at 75 to 100 U/kg subcutaneously three times per week until the PCV is in the low normal range (35%), then reduce dose and frequency to 50 to 75 U/kg subcutaneously two times a week. It is important to monitor PCV for the first 60 to 90 days to detect development of anti-erythropoietin antibodies as noted by a decline, rather than an increase in PCV (at comparable TS). If this occurs, cease erythropoietin treatment immediately. The cat may be transfusion dependent for two to four months until anti-erythropoietin antibody levels decrease. It is also important to administer iron at the start of the regimen and until the cat's appetite improves. While the risk of anti-erythropoietin antibodies developing exists, most cats will enjoy the benefits of an increased PCV.

Recently, darbepoetin has been receiving attention as an alternative to erythropoietin, and it may be less antigenic and can be given less frequently. The dose is 0.45 µg/kg/week, but it's also possible to convert the current erythropoietin dose (Table 2).

Drug Dose Adjustments in Renal Insufficiency

For a drug that relies on the kidneys for drug clearance, a loss in renal function will proportionately decrease drug excretion. Thus, a 75% loss in renal function results in a 75% loss in renal drug clearance. Dosage adjustments can be made from estimates in the loss of renal function. The most exact method of assessing renal function is to measure creatinine clearance as an estimate of GFR.

A less precise but more practical approach is to make a dose adjustment based on serum creatinine (Figure 1). Remember that this type of dose adjustment estimate is risky in geriatric pets, compared with younger pets, because serum creatinine is affected by muscle mass. Therefore, a geriatric animal with decreased muscle mass and renal function may have a falsely low serum creatinine level.

Table 2. Equivalent Erythropoietin and Darbepoetin Dosages*

Erythropoietin (units/week)	Darbepoetin (µg/week)
< 1,500	6.25
1,500 to 2,499	6.25
2,500 to 4,999	12.5
5,000 to 10,999	25
11,000 to 17,999	40
18,000 to 33,999	60

* Total weekly doses

Figure 1. Drug dose adjustment based on serum creatinine levels.

New dose =

$$\text{old dose} \times \frac{\text{normal serum creatinine level}}{\text{patient's serum creatinine level}}$$

New interval =

$$\text{old interval} \times \frac{\text{patient's serum creatinine level}}{\text{normal serum creatinine level}}$$

DIETARY RESTRICTION OR SUPPLEMENTATION

Protein. Dietary protein restriction does not ameliorate progression of renal insufficiency in cats based on results in the remnant kidney model in cats.[4] But it's important to note that the remnant kidney model does not reflect or emulate natural disease.

The effectiveness of a therapeutic renal food has been examined in cats with Stages 3 and 4 chronic kidney disease by a randomized, controlled clinical trial.[5] This study examined the benefits of feeding a renal food vs. a standard feline maintenance food to cats with chronic kidney disease. Other than being randomly assigned to either the renal or maintenance food, cats were managed in an identical manner with respect to other treatment interventions. Cats fed the maintenance food had significantly more uremic episodes (22%) than cats fed the renal food (0%). A significant reduction in renal-related mortality was observed in cats fed the renal food. Importantly, significant adverse effects of feeding the renal food were not detected in the study.[6]

However, in acute renal failure, and in mild to moderate chronic renal insufficiency, dietary protein restriction may limit the kidney's compensatory response to injury. Protein restriction may lead to protein malnutrition, which impairs the immunologic response and decreases hemoglobin production, thus promoting anemia, decreasing plasma protein levels, and promoting muscle wasting. Inadequate protein also decreases urinary excretion of magnesium, which may result in calcium phosphate precipitation in the kidneys. Watching for evidence of protein-calorie malnutrition should include monitoring for weight loss, hypoalbuminemia, poor hair coat quality, and muscle wasting.

Dietary treatment of moderate to severe chronic renal insufficiency (serum creatinine > 5 mg/dl, BUN > 75 mg/dL in the rehydrated cat) is not controversial; restriction of both protein and phosphorous are required to avoid uremic complications. Benefits of protein restriction are related to non renal effects (toxins affect organs other than kidneys). Using protein sources of high biological value is important. Protein restriction may be especially harmful in renal patients who are inappetent, as a sustained calorie deficit causes body proteins to be catabolized to supply calories and the nitrogenous end products of this process will further accentuate uremic signs. Inappetence is an indication for avoiding protein-restricted diets.

Phosphorus. It is important to restrict phosphorus in moderately azotemic patients; this is more important than protein restriction to survival in the canine remnant kidney model and has been shown to produce less severe renal lesions in the feline remnant kidney model. The dose of intestinal phosphate binders cited in the literature may be too low (an example is Aluminum hydroxide: Initially at 30 to 90 mg/kg per day. Dosage must be individualized: increase the dose as necessary to produce consistent, serum phosphorus levels within the normal range. If using calcium-based intestinal phosphate binders, monitor serum calcium levels carefully and switch to or combine them with aluminium-based phosphate binders if necessary. For these agents to be effective, they must be given with food; they act by binding the phosphorus in the ingested food and making it unavailable for absorption.

Potassium. Because hypokalemia may induce a reversible, functional decline in GFR, potassium supplementation is warranted for cats with chronic renal insufficiency and hypokalemia, even in the absence of overt clinical signs. Polyuria results in increased urinary potassium loss as well. Dietary acidification causes intracellular potassium to shift to the extracellular space, raising serum potassium levels but not reflecting total body potassium levels. Thus, metabolic acidosis appears to be a major risk factor for hypokalemia and should be rectified early in the management of hypokalemia. Potassium supplementation (potassium gluconate at 2 to 4 mEq orally twice a day) may be considered after acidosis is corrected.

Calcitriol. Calcitriol use is still controversial in that some researchers feel that its use is more urgent than others. Calcitriol advocates suggest that it should be started at 2.5 to 3.5 ng/kg/day orally in early renal insufficiency when serum creatinine is 2 to 3 mg/dL, urine specific gravity is compatible with chronic renal insufficiency, and phosphorus is < 6 mg/dL. In these patients, the parathyroid hormone levels are often normal; calcitriol is used to prevent hormone levels from increasing to slow progression of the chronic renal insufficiency and prevent clinical signs related to parathyroid hormone toxicity. In patients with a serum creatinine of > 3 mg/dL and serum phosphorous of < 6 mg/dL, the dose is 3.5 ng/kg/day orally. A baseline parathyroid hormone measurement in these patients is useful because the levels are commonly elevated and may require higher doses of calcitriol. It is imperative to have good client compliance—carefully monitor ionized calcium and parathyroid hormone levels. The Ca times P product must be < 60.

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POLYURIA / POLYDIPSIA: AN INTERNIST'S PERSPECTIVE

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DEFINITIONS

Polydipsia (PD) = water intake > 100 mL/kg/day
Polyuria (PU) = urine output > 50 mL/kg/day

It is important when owners present patients for excessive, inappropriate, or abnormal urination to distinguish PU-PD from other abnormalities in urination such as incontinence or pollakiuria. A careful history in combination with a urine specific gravity can usually confirm the presence of true PU/PD.

PHYSIOLOGY

Plasma osmolality is maintained within very narrow ranges. Total body water is adjusted to keep it in balance with the serum sodium concentration. Under normal circumstances, body water rarely varies by more than 1% to 2%. Water intake is controlled via thirst mechanisms and water output is controlled through secretion of vasopressin. Water is lost through urine, feces, and respiration. The ability of the kidneys to concentrate urine is very critical in the maintenance of water balance. Some water is always lost into the urine.

Changes in circulating volume and osmolality trigger osmoreceptors and baroreceptors. The release of angiotensin II and vasopressin (= AVP = antidiuretic hormone = ADH) is then triggered. These compounds stimulate thirst and increased urine concentration respectively. AVP promotes the reabsorption of solute free water in the distal and collecting tubules.

MORE DEFINITIONS

Solute diuresis (osmotic diuresis). This occurs when there are large amounts of a poorly reabsorbed solute such as glucose, mannitol, or urea. When these compounds are present in the glomerular filtrate, fluid resorption from the proximal tubules is impaired. This overwhelms the nephron's ability to resorb water, leading to large volumes of urine with low osmolality.

Water diuresis. This occurs due to the absence of AVP. There is limited reabsorption of solute-free water in the distal and/or collecting ducts leading to large volumes of urine with low osmolality.

DIFFERENTIAL DIAGNOSES

There are many, many causes of PU/PD. These causes can be classified according to their underlying pathophysiology:

Primary Polydipsia

- Psychogenic
- Liver disease
- Neurologic disease
- Hyperthyroidism

Osmotic Diuresis

- Diabetes mellitus
- Primary renal glucosuria
- Renal failure (acute and chronic)

Central Diabetes Insipidus (CDI) (any disturbance or injury to the hypothalamus and/or pituitary is a potential cause)

- Idiopathic
- Hyperadrenocorticism
- Trauma
- Neoplasia
- Cysts
- Inflammation

Nephrogenic Diabetes Insipidus (NDI)

- Primary NDI
- Renal failure
- Pyelonephritis
- Hyperadrenocorticism
- Hypoadrenocorticism
- Hyperthyroidism
- Hepatic insufficiency
- Pyometra
- Hypercalcemia
- Hypokalemia
- Renal medullary solute washout
- Drugs/toxins
- Diet

In adult dogs, the most common causes of PU/PD include diabetes mellitus, kidney disease, liver disease and hyperadrenocorticism.

In adult cats, the most common causes of PU/PD include diabetes mellitus, kidney disease, and hyperthyroidism.

DIAGNOSTIC APPROACH

The initial assessment of the PU/PD patient must include a complete history, including diet and any possible medications, thorough physical examination, urinalysis (UA), CBC, and biochemical profile. These initial steps often elucidate the underlying cause of the PU/PD or at least will suggest the next appropriate diagnostic steps. A urine culture, regardless of the urine sediment, should also be considered as part of the initial work-up of the PU/PD patient for two reasons. 1) Pyelonephritis, which may be occult, can be the underlying cause for the PU/PD, and 2) many of the diseases that cause PU/PD also make the patient prone to urinary tract infections.

In cats, thyroid hormone levels should be determined.

Adrenal function testing should be considered in the canine patient presenting for PU/PD. An ACTH stimulation test is advised as the initial test of adrenal function because it can detect both hypoadrenocorticism and hyperadrenocorticism (naturally occurring and iatrogenic).

Another test to consider fairly early in the work-up of dogs presenting for PU/PD are pre- and postprandial bile acids. While there are typically clues on the history and minimum database suggestive of liver disease, this is not always the case. Liver disease should be thoroughly ruled out.

Abdominal ultrasound is useful as a screening test to look for evidence for many of the potential causes of PU/PD (renal failure, liver disease, pyelonephritis, adrenal disease, etc.).

The above tests (as appropriate to species) should all be performed before pursuing a water deprivation test. A water deprivation test determines whether the patient cannot produce AVP (central diabetes insipidus), cannot respond to AVP (nephrogenic diabetes insipidus) or suffers from psychogenic polydipsia. Given the majority of cases of PU/PD result from secondary nephrogenic diabetes insipidus, it is prudent to rule out those diseases first before proceeding to any form of water deprivation test.

Modified Water Deprivation Test

First, have the owner monitor water intake for a few days at home. Three days before the in-hospital water deprivation test, have the owner restrict the water to 120 mL/kg/day. Two days before the in-hospital water deprivation test, have the owner restrict the water to 100 mL/kg/day. One day before the in-hospital water deprivation test, have the owner restrict the water to 60 to 80 mL/kg/day. This should help re-establish the medullary concentration gradient. Depending on how much the patient has been drinking, this may need to be done even more slowly.

The in-hospital portion of the test is then begun. Take away all food and water. Empty the patient's bladder and measure the urine specific gravity and osmolality if available. Measure the patient's baseline packed cell volume (PCV), creatinine, BUN, and serum osmolality if available. Do not proceed if there is any evidence of azotemia or severe systemic disease. Every hour thereafter until the test is done, the following items need to be monitored: patient's weight, urine specific gravity and osmolality (empty the bladder hourly), patient's overall well-being and hydration. An indwelling urinary catheter should be considered to make it easier to monitor urine. Periodic rechecks of serum osmality and BUN should also be performed.

The test is finished when: 1) The urine concentrates to ≥ 1.030, 2) The patient loses 5% of their initial body weight, or 3) The patient becomes dehydrated, azotemic, or ill.

If the patient has concentrated their urine at this point, the diagnosis is psychogenic polydipsia.

If the patient hasn't concentrated their urine, then exogenous AVP 0.55 U/kg (5U maximum) should be administered intramuscularly. Empty the bladder every 30 minutes for 2 hours and check the urine specific gravity and osmolality if available. Patients with central diabetes insipidus should concentrate their urine by the end of 2 hours. In place of administering aqueous AVP, a synthetic vasopressin analogue (DDAVP) can be given. Give 4 drops of the intranasal solution into the conjunctival sac or 10 to 20 µg of the intranasal or parental solution subcutaneously or intravenously. Urine specific gravity needs top be evaluated hourly for the first 8 hours and then at 12 and 24 hours. Patients with central diabetes insipidus should concentrate their urine following administration of DDAVP. Urine remaining hyposthenuric or isosthenuric is consistent with nephrogenic diabetes insipidus.

Central diabetes insipidus can be either partial or complete. Patients with partial CDI will show a slight improvement in their urine concentrating ability following water deprivation and further concentration following the administration of AVP.

DDAVP Response Test

An alternate to the water deprivation test is to have the owner administer DDAVP at home. The owner should first quantify daily water intake for a few days and a baseline urine specific gravity should be obtained. Then the owner should begin administering DDAVP, either 1 to 4 drops of the intranasal solution into the conjunctival sac every 12 hours or 0.1 mg orally every 12 hours. Urine specific gravity should be rechecked after 5 to 7 days to evaluate for any increase in concentration. In patients with complete CDI, the owners should notice a dramatic decrease in water intake as well.

Aquaporins

Aquaporins are membrane channels, which serve as water channels. The urinary excretion of aquaporin-2 correlates with plasma vasopressin levels. Measurement of aqauporin-2 in the urine may help differentiate among the causes of PU/PD in the future.

TREATMENT

Psychogenic Polydipsia

This is the only cause of PU/PD wherein it is appropriate to restrict access to water. Behavior modification may also be of benefit in some cases.

Central Diabetes Insipidus

It is not necessary to treat CDI as long as unlimited access to water is always provided. For owners who wish to treat, DDAVP is the treatment of choice for complete CDI and can also treat partial CDI. DDAVP can be administered into the conjunctival sac (1 to 4 drops of the intranasal solution twice daily) or 0.05 to 0.1 mg orally two to three times daily. It is recommended to not allow the pet to drink large amounts of water immediately following administration. Concern exists for the patient consuming vast quantities of water and then being unable to excrete it, resulting in water intoxication. This has not been seen in clinical cases. A low-salt diet should be fed in conjunction with DDAVP.

Chlorpropamide has been suggested as a treatment for partial CDI. It is a sulfonylurea thus may cause hypoglycemia. It is believed to enhance the renal response to ADH. It may take one week to be effective.

The suggested dose is 10 to 40 mg/kg PO once daily. Electrolytes and blood glucose should be monitored.

Interestingly, thiazide diuretics have also been suggested as a treatment for either CDI or NDI. Thiazides inhibit sodium reabsorption in the ascending Loop of Henle, reducing the total body sodium concentration. This then leads to contraction of the extracellular fluid volume, which in turn causes increased salt and water resorption in the proximal renal tubules. The fluid reaching the distal tubules now has a lower sodium concentration and less osmotic pressure, finally resulting in more water resorption and less urine produced. Thiazide diuretics are only useful for mild cases. A low sodium diet should be fed in conjuction with their use. The dose for chlorothiazide is 20 to 40 mg/kg PO bid.

A low sodium diet can be used as the sole therapy for either CDI or NDI.

Nephrogenic Diabetes Insipidus

The focus of treatment should be on the identified underlying cause. Thiazide diuretics may reduce the amount of urine produced in primary NDI.

References are available from the author upon request.

FELINE IDIOPATHIC CYSTITIS: CURRENT INFORMATION AND HOW IT APPLIES TO TREATMENT

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PATHOPHYSIOLOGY

Histologic changes associated with feline idiopathic cystitis (FIC) are generally nonspecific, and may include an intact or damaged urothelium with sumbmucosal edema, dilation of submucosal blood vessels with marginated neutrophils, submucoal hemhorrhage, and sometimes increased mast cell density. Based on our experience, no correlation between histology and cystoscopic lesions and clinical signs appears to exist in cats. In fact, owners have reported complete remission of lower urinary tract signs in cats with FIC, but visualization of their bladder revealed glomerulations and other abnormalities.

Additional studies in cats with FIC have shown increased leakage of ions across the urothelium and urea leakage in non-hydrodistended bladders. Marked increases in permeability after hydrodistention were also present. We have also documented increased bladder permeability to sodium salicylate in cats with FIC. Furthermore, bladder permeability appeared increased in cats given IV sodium fluorescein.

Clinical signs of FIC can wax and wane and appear to be exacerbated by stressful circumstances. In previous studies in cats with FIC, we found they had a significant increase in tyrosine hydroxylase (TH) immunoreactivity in the brainstem (locus coerules) as well as the paraventricular nucleus of the hypothalamus. TH is the rate-limiting enzyme of catecholamine synthesis. The increased TH immunoreactivity observed in the LC of cats with FIC may provide a clue to the observation that clinical symptoms of FIC follow a waxing and waning course, and can be aggravated by environmental stressors. Because of these findings, we prospectively evaluated various catecholamines in 13 FIC and 12 healthy cats. All cats were subjected to an acute, moderate stressor for eight days. During that time period, we compared serum fluorescein concentrations to evaluate bladder permeability, and urine coritsol:creatinine to evaluate the hypothalamic-pituitary-adrenal axis. In a subset of cats, catecholamine concentrations [CCE] were also analyzed. After 8 days of a moderate stressor, all cats were moved to an "enriched" environment and testing was once again repeated to investigate this form of therapy. Our results showed that fluorescein concentrations were significantly higher in FIC cats at all times. In the group of cats where plasma [CCE] were available, plasma DOPA, norepinephrine (NE) (Figure 1), and dihydroxyphenylglycol (DHPG) concentrations were significantly increased in FIC cats at all times (*P*<0.05), no differences between groups were identified in cortisol:creatinine. Therefore, we concluded that FIC cats appear to have altered bladder permeability, which was worse during the initial stress. The marked increment in [DOPA] suggests the possibility of a stress-induced increase in activity of tyrosine hydroxylase (TH), the rate-limiting step in CCE synthesis. In contrast, no effects on urine cortisol:creatinine were identified, suggesting an uncoupling of these two parameters of the stress response. Similar findings have been reported in human patients with chronic pelvic pain, and other comorbid conditions.

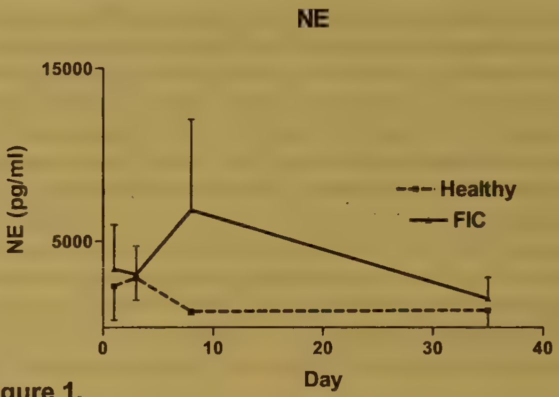

Figure 1.

Enhanced stimulus-induced local NE release from the bladder, could lead to a functional desensitization of central alpha-2 adrenoceptors (α-2 AR) in cats with FIC. In the brainstem, α-2 agonists inhibit NE release, whereas in the spinal cord they inhibit transmission of nociceptive input to the brain. To further test this hypothesis, we evaluated the functional sensitivity of the α-2 AR in cats with FIC by evaluating their response to the selective α-2 AR agonist, medetomidine. These studies were carried out under the same stress protocol we measured catecholamine concentrations. If the post-synaptic α-2 ARs are normal, one would expect a decrease in heart rate and increase in pupil size after medetomidine administration. The decline in HR following medetomidine administration was significantly greater in healthy cats compared with cats with FIC, although this difference was attenuated by day 35 (p=0.05, Table 1). The increase in pupil diameter following medetomidine administration was significantly greater in healthy cats compared to FIC cats. We did not see any significant differences in post synaptic α2-AR function when evaluating sedation. Electrical field stimulation studies of bladder strips from FIC cats

Table 1.

Percent Change in HR after Medetomidine Administration	FIC (mean ± SD)	Healthy (mean ± SD)
Day 1	23%±15%*	34%±10%
Day 3	15%±14%*	37%±12%
Day 8	24%±9%*	32%±13%
Day 35	20%±10%	26%±16%

revealed that atipamezole, an α2-AR antagonist, did not alter the relaxing effect of NE, further suggesting that α2-AR's are down-regulated in this disease.

In addition to the sympathetic nervous system, abnormalities in the hypothalamic-pituitary-adrenal axis (HPA) have also been observed in cats with FIC. After a high dose (125 µg) of synthetic ACTH was administered, cats with FIC had significantly decreased serum cortisol responses compared with healthy cats (Figure 2). Although no obvious histologic abnormalities were identified, the areas consisting of the zonae fasciculata and reticularis were significantly smaller in sections of glands from cats with FIC than from healthy cats. Therefore, it appears that while the sympathoneural system is fully activated in this disorder, the HPA axis is not.

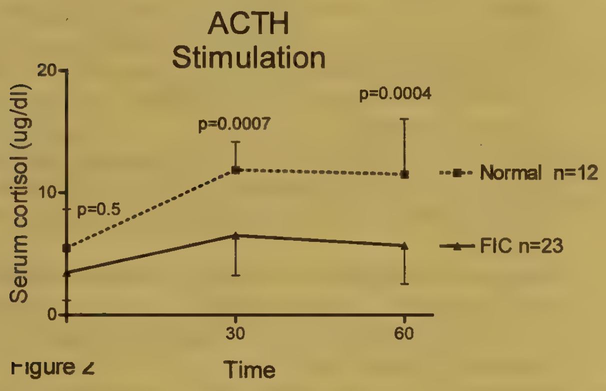

Figure 2.

The pathophysiology of FIC is likely involves complex interactions between a number of body systems. Abnormalities are not localized just to the bladder, but are present in the nervous, endocrine, and even cardiovascular systems. How these systems communicate and manifest as FIC in some cats, but not in others remains to be determined. It is important for clinicians to understand that this syndrome is not just a "bladder disease" amenable to simple diet or drug therapies in order to better treat their patients.

APPROACH TO THE PATIENT DIAGNOSTICS

Because FIC is a diagnosis of exclusion, diagnostics should be performed to rule out other causes of lower urinary tract signs (LUTS) mentioned above. Urolithiasis can occur in approximately 12% to 15% of cats with LUTS and an abdominal radiograph which includes the entire urinary tract should be performed. Less than 2% of young (<10 years of age) cats have true bacterial cystitis, so urine culture is a low yield test. Quantitative urine culture should be performed in all cats with recurrent (>2 episodes) LUT signs. The possibility of a urinary tract infection increases with age, perineal surgery, in the presence of cystic calculi, and dilute urine. A contrast cystogram and urethrogram can be helpful to better evaluate for the presence of non-radiopaque calculi and other lesions such as mass lesions, blood clots, and strictures in those cats with recurrent episodes. If clinical signs continue, despite therapy, an abdominal ultrasound, double contrast cystourethrogram, and/or cystoscopy can be performed to be sure no other lesions in the lower urinary tract were missed. Contrast studies are especially indicated in elderly cats (>10 years of age) where FIC is not as likely.

TREATMENT OF FIC

When a cat presents with LUTS, analgesic therapy seems appropriate for the acute management of the disease. Providing analgesia with non-steroidal anti-inflammatory agents such as carprofen and ketoprofen, or butorphanol or more potent opioids such as fentanyl (patches) has been suggested, but no studies have been reported to date, and many drugs are not approved for these uses. We believe that breaking the chronic pain-inflammation cycle may be important in the management of at least some cats with severe disease. During acute flare-ups we generally prescribe some form of analgesia such as butorphanol combined with a short-term tranquilizer such as acepromazine.

MULTIMODAL ENVIRONEMENTAL MODIFICATIONS

Based on our previous findings where catecholamines decreased after environemental modifications in research cats, we have evaluated client-owned cats with idiopathic cystitis implementing multimodal environmental modification (MEMO) as the sole management strategy. In this observational study we evaluated forty- six client owned indoor-housed cats with idiopathic cystitis, diagnosed based on a history of recurrent LUTS and evidence of absence of urolithiasis or bacterial urinary tract infection. In addition to their usual care, clients were offered recommendations for MEMO based on a detailed environmental history. Cases were followed for 10 months by client contact to determine the effect of MEMO on LUTS and other signs. Significant ($P<0.05$) reductions in LUTS, fearfulness, nervousness, signs referable to the respiratory tract, and a trend ($p<0.1$) toward reduced aggressive behavior were identified. These results suggest that MEMO is a promising adjunctive therapy for indoor-housed cats with LUTS.

We follow a staged approach to therapy which begins with client education and MEMO. If a patient relapses, these topics are thoroughly reviewed and additional changes are implemented. In multi-cat houses, cats also interact with each other. Addressing inter-cat issues seems very important in the management of this disease as well.

Dietary Therapy

Some dietary modifications may reduce the risk of recurrence of LUT signs in affected cats. Efforts to acidify the urine using dry foods have no demonstrated value in treatment of cats with FIC. There is no known benefit of acidifying the urine or restricting magnesium in cats with FIC. We do encourage increasing water intake, and consumption of a canned food is one way to accomplish this. To avoid the potential stress of being confronted with an unfamiliar diet, we recommend beginning the new canned food alongside the original diet. We reported that LUT signs recurred in only 11% of affected cats during one year of feeding the canned formulation of a dietary product designed to result in production of slightly acidic urine. Recurrence occurred in 39% of cats fed the dry formulation of the same food, suggesting that both constancy and consistency (i.e., increased water intake) may be important, but the reasons for this effect remain to be determined.

Pheromones and Drug Therapy

Pheromones are fatty acids that seem to transmit highly specific information between animals of the same species. Although the exact mechanisms of action are unknown, pheromones reportedly induce changes in both the limbic system and the hypothalamus that alter the emotional state of the animal. Feliway® (Ceva Sante Animale, Libourne, France), a synthetic analogue of this naturally occurring feline facial pheromone, was developed in an effort to decrease anxiety-related behaviors of cats. Although not specifically tested in cats with FIC, treatment with this pheromone has been reported to reduce the amount of anxiety experienced by cats in unfamiliar circumstances, a response that may be helpful to these patients and their owners. Increased grooming and food intake in hospitalized cats also has been reported with the use of Feliway.

We have used amitriptyline (a tricyclic antidepressant (TCA)) in uncontrolled trials to successfully decrease clinical signs of severe, recurrent FIC. Amitriptyline (Elavil®, 2.5–5 mg per cat SID), may provide analgesia by inhibition of NE reuptake at noradrenergic nerve terminals, and possibly due to inhibition of a wide range of nociceptive neurons in the spinal trigeminal nucleus. Urine retention through anticholinergic effects of the TCAs may result. Findings in a series of cats with severe FIC showed that the clinical signs of some cats were reduced during amitriptyline treatment during a 12-month period. Improvement in clinical signs was not always accompanied by improvement in the cystoscopic appearance of the bladder.

Clomipramine (Clomicalm®, veterinary label; and Anafranil®, human label) is also a tertiary amine like amitriptyline, but has more selectivity for blocking the reuptake of 5-HT. We have prescribed this in recurrent cases of FIC with anecdotal improvements in some patients. Other drugs such as fluoxetine (Prozac®) has been reported to help cats with inappropriate urinations with variable success rates. Fluoxetine was used to help decrease the rate of urine marking after environmental alterations such as litter box hygiene and appropriate cleaning strategies.

We do not recommend amitriptyline for acute treatment of FIC since it has been shown to have minimal to no benefit in the short- term resolution of signs in cats with FIC. We reserve all the TCAs, as well as the selective serotonin reuptake inhibitors for recurrent, severe cases. These drugs need to be used only after environmental strategies, diet changes (if necessary), and behavior modifications have failed. Furthermore, it is our opinion that these drugs should then only be used in conjunction with the above-mentioned therapeutic strategies for optimal effects.

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CAUDA EQUINA: WHAT TO DO?

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Motion is the normal lumbar spine is greatest at the lumbosacral joint. In some dogs, abnormal motion probably leads to degenerative changes such as spondylosis deformans, osteophyte proliferation, and soft tissue overgrowth of the joint capsules. These degenerative changes appear to reduce the overall range of motion and clinical problems may arise due to subsequent compression of neural structures in the vertebral canal and intervertebral foramina. A number of abnormalities may combine to cause compression of the cauda equina or L7 nerve roots. These include stenosis (multilevel) of the vertebral canal; Hansen type II disk herniation at the L7-S1 intervertebral space; subluxation, osteophytosis or thickening of the articular processes; epidural fibrosis; soft tissue proliferation, usually of the joint capsule or ligamentous structures; vascular compromise of the spinal nerves; osteochondrosis of the sacrum; and instability and misalignment between L7 and S1.

Larger-breed dogs, particularly German shepherd dogs, are affected most frequently although signs are also reported in small dogs. Tumors and fractures should be considered in the differential diagnosis. Diskospondylitis also occurs at the lumbosacral junction.

The choice of treatment is mainly based on recognition of the cause of the disease using the clinical signs, the neurologic examination, and ancillary tests.

CLINICAL SIGNS

Lumbosacral lesions can cause pelvic limb gait abnormalities, lameness, or lower motor neuron (LMN) neurologic deficits. Pain is common but additional signs vary depending on the nature and severity of the neurologic impairment. There may be pain with no deficits; mild paresis with proprioceptive deficits; or paraparesis, tail paralysis, and incontinence. Limb signs include lameness or sciatic deficits affecting the caudal thigh muscles and those distal to the stifle. Incontinence results from pelvic and pudendal nerve dysfunction. Urinary incontinence is usually LMN in nature with dribbling of urine and a bladder that is easily expressed by manual pressure.

DIAGNOSIS

Clinical signs may be vague in some dogs, which makes accurate diagnosis difficult. A **thorough physical, orthopedic, and neurologic examination** is essential, along with a rectal examination. In view of the difficulty in interpreting some of the ancillary diagnostic tests, the clinical signs may provide the main basis for reaching a diagnosis.

The patellar reflex may also appear exaggerated if sciatic nerve function is depressed. This phenomenon of "pseudohyperreflexia" must be differentiated from the increased reflex that occurs with upper motor neuron (UMN) deficits seen with lesions cranial to the L4 segment.

Hyperesthesia is a frequent finding and the hindquarters should be palpated carefully to locate the focus of pain. If lameness or weakness worsens with exercise and resolves to some degree with rest, then they may be due to neurogenic claudication, a condition well recognized in humans. This is due to failure of arterial vasodilation in affected nerve roots during exercise.

Clinical **electrophysiological studies** are useful to confirm LMN disease and nerve root dysfunction. Electromyography of the limbs, tail, and perineum may reval spontaneous activity, which is consistent with LMN involvement. However, a normal electromyogram does not eliminate the possibility of lumbosacral disease.

When a cauda equina is **suspected radiographs** of the lumbosacral area is mandatory. It is advisable that the patient be anesthetized or sedated heavily when radiographing the lumbosacral joint. The value of flexed and extended positional survey radiographs appears limited. The main role of survey radiographs is to rule out neoplasia, trauma, and diskospondylitis. Many clinically normal dogs have radiographic abnormalities of the lumbosacral junction. Conversely, occasional dogs with lumbosacral disease will have normal survey radiographs.

Myelography is particularly useful in dogs that might have a spinal cord lesion. The subarachnoid space extends beyond the lumbosacral junction in about 80% of dogs. Myelography can therefore be useful to assess the low lumbar region as well as the rest of the spinal cord.

Computed tomography (CT) is particularly useful as it shows clearly the vertebral canal, lateral recesses, intervertebral foramina, and articular processes in cross-sectional images (Figures 1, 2, 3, and 4). Reformatting can be used to create dorsal and sagittal images and facet joint subluxation may be visible using bone window images or 3D reconstructions. CT can also be used for dynamic studies and is helpful when performed after surgery. The primary abnormalities visible on CT are a replacement of epidural fat with soft tissue density, which often represents epidural fibrosis and multilevel compression. Use of intravenous contrast may improve surgical decision-making by identifying compressed tissues, which tend to enhance. Some CT findings, such as loss of epidural fat, may not be of clinical significance in older animals. In contrast to MRI, CT offers lower cost and thinner slice thickness along with better discrimination of bone spurs, articular process disease, soft tissue calcification and soft tissue gas opacities. Scans should include at least the L6 vertebral body and ideally, additional images should also be made through the L4-5 and L5-6 disk spaces.

MRI provides better soft tissue resolution than CT as well as an ability to acquire images in multiple planes without image degradation; earlier detection of disc degeneration and evaluation of the entire lumbar spine in a single sagittal examination. Slice thickness is often greater than for CT, however, which increases volume

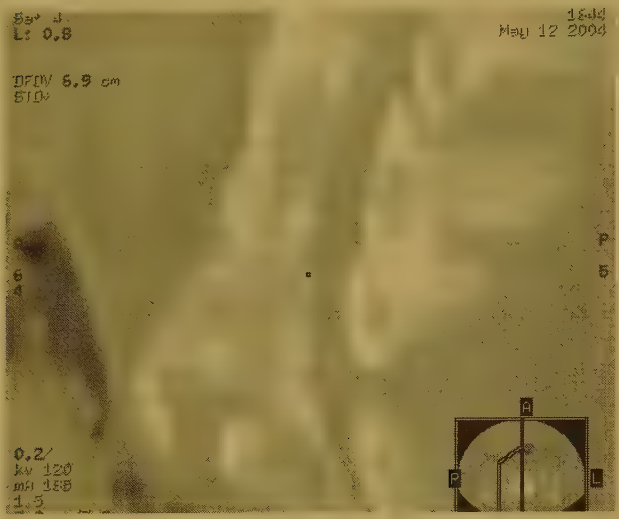

Figure 1. Reformatted lumbosacral view with bone narrowing of the foramen.

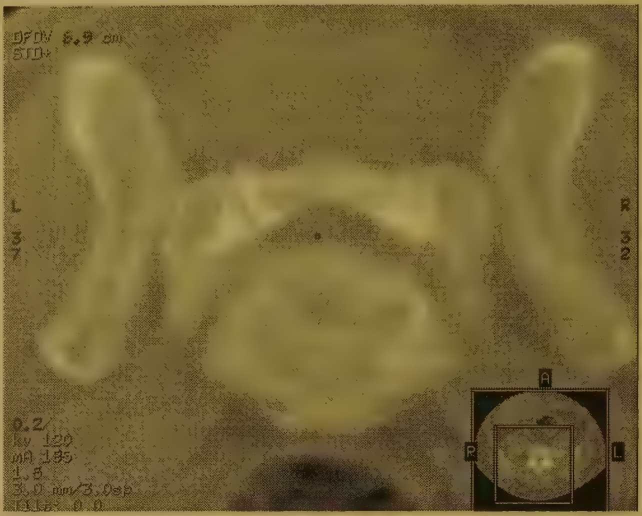

Figure 2. L7-S1 axial CT showing the filter showing L7-S1 spondylosis.

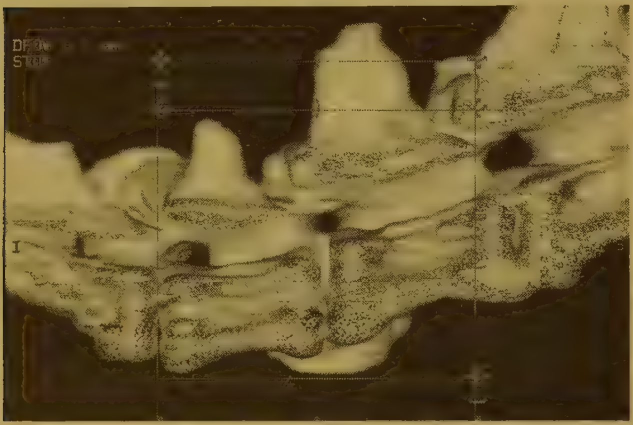

Figure 3. 3D reconstruction (left half) demontrasting L6-L7 stenosis.

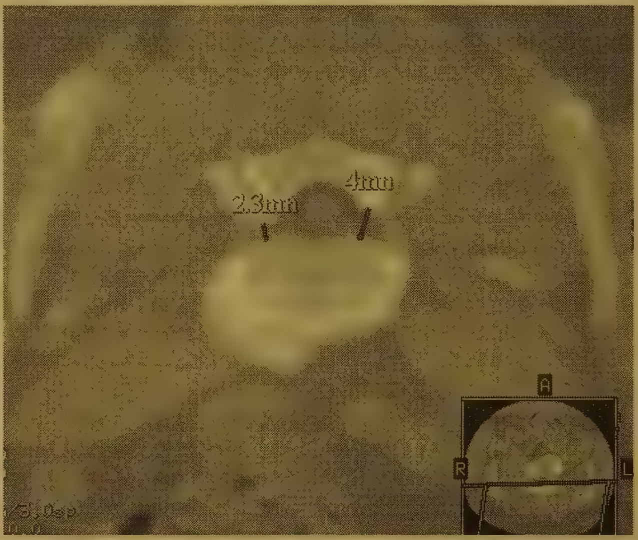

Figure 4. Same dog as Figure 3 showing the narrowing of the left L6-L7 foramen.

averaging artifacts. Transverse images provide the best visualization of disk or foraminal anatomy. They also reveal lesions in a foramen that cannot be detected by myelography or epidurography. Sagittal views made with the spine in flexion and then extension help to identify a dynamic component to the compression. One potential disadvantage of MRI is over-diagnosis.

The choice of diagnostic tests is largely dependent on availability and clinician preference. Physical and neurological examination, survey radiography, CSF sampling at both the cerebello-medullary cistern (CMC) and lumbar sites and clinical electrophysiology are recommended. Imaging with CT or MR is done when available as they provide cross-sectional images. CT and MRI can also be used to compare the degree of compression with the spine in flexed and extended positions. Either myelography or MRI should be performed if the dog has signs of spinal cord disease. If CT or MRI is not available, myelography is performed followed by diskography and epidurography if necessary. Some lesions detected by CT or MRI do not cause clinical signs and this must be considered prior to instituting treatment. A herniated disk is detected in a high proportion of people who have never had spinal pain and so imaging alone, both in dogs and in humans, should not serve as confirmation of a clinical diagnosis. Electrophysiological testing provides an additional means of independent confirmation of lesions.

TREATMENT

Nonsurgical Treatment

Most dogs are treated initially with rest and anti-inflammatory medication. This may be successful if pain is the main clinical sign; 3 to 4 months of exercise restriction produced improvement in 50% of the dogs. Such a course is seldom effective in working dogs and signs often recur when normal activities are resumed.

Surgical Treatment

Surgical treatment is indicated when nonsurgical treatment has failed; in working dogs; and in those with pain or neurologic deficits. Further indications for surgery include CT or MR findings of increased soft tissue suggestive of epidural fibrosis, especially if it enhances with contrast. The choice of surgical procedure is then between dorsal laminectomy, distraction and fusion, or a combination of the two. Definitive criteria for these procedures are lacking. Laminectomy alone is not effective for dogs with chronic incontinence. Fusion alone may be insufficient for dogs with neurologic deficits or severe pain. These presentations warrant combined dorsal laminectomy and fixation-fusion. Additional indications for distraction and fusion include a marked change in the degree of compression between flexion and extension or a telescoping of the facets, which suggest instability.

Dorsal Laminectomy

Decompression of the cauda equina and spinal nerves can be achieved by dorsal laminectomy, which can be combined with foraminal decompression or even facetectomy. The annulus fibrosus should be excised once the cauda equina is retracted laterally when there is marked bulging of the disk. Routine fenestration may also be warranted. Any redundant joint capsule should also be resected. Laminectomy often provides rapid relief of pain with improvement of mild gait abnormalities and minor neurologic deficits. It does not address instability if this is a contributing factor. Decompression by laminectomy can be combined with fixation and fusion. As dogs with incontinence of more than 6 weeks duration respond poorly to laminectomy alone they should also undergo fixation and fusion. Epidural fibrosis is a common finding.

Foraminal Decompression or Facetectomy

An increase in soft tissue within the foramen, loss of epidural fat, and facet osteophytosis are indicators of probable radiculopathy. Contrast enhancement after CT or MRI further increases preoperative suspicion of foraminal disease. Together with radicular pain and delayed late waves; these features are indicators for some form of foraminal decompression. The laminectomy can be simply undercut or widened over the foramen and any osteophytes can also be removed by undercutting. However, the foramen can be difficult to examine fully until the facet is removed. The risks and benefits of facetectomy are unclear as is the need for subsequent stabilization. Lumbosacral stiffness is decreased markedly after bilateral facetectomy.

Dorsal Fusion-Fixation

There are a number of similarities between lumbosacral disease and caudal cervical spondylomyelopathy. A rationale can therefore be made for lumbosacral distraction and stabilization. The principle is the same: namely, to open the vertebral canal and intervertebral foramen, relieve pressure on neural tissues, and prevent abnormal motion. Distraction of the dorsal aspect of L7 and S1 is achieved using screws placed though the articular processes of L7-S1 and into the body of the sacrum. Fusion is promoted by removing the articular cartilage from the facet joints and by a cancellous bone graft. This can be combined with dorsal laminectomy, especially for dogs with marked neurologic deficits, severe pain, or a large disk herniation.

Laminectomy provides rapid relief of pain in most dogs. Similarly, lameness and mild neurological deficits usually improve rapidly. More severe deficits probably carry a less favorable prognosis. Few studies document long-term follow-up periods beyond 1 year show overall success rates from 73% to 93%. The presence of fecal incontinence and both the presence and the duration of urinary incontinence prior to surgery, are negative prognostic factors in dogs with lumbosacral disease. Incontinence for longer than 6 weeks carries a guarded prognosis.

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STROKE IN DOGS — WHAT DO WE KNOW?

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Cerebrovascular accidents (CVA) are one of the major causes of disability among human adults. Previously considered uncommon, CVA are increasingly recognized in dogs or cats with the advances of neuroimaging. Most types of CVA that are seen in humans have been documented in dogs. Recovery from cerebrovascular disorders in animals is probably more spectacular than in humans because animals have a less prominent pyramidal system. A "stroke" is a suddenly developing focal neurological deficit resulting from a cerebrovascular accident. The causes of strokes can be divided into two basic groups: (1) obstruction of the blood vessels leading to ischemia, and (2) rupture of blood vessel walls leading to hemorrhage.

The central nervous system (CNS) requires a continuous supply of glucose and oxygen to sustain its high expenditure of energy. The transportation of these fuel molecules requires sufficient blood flow through a cerebral vasculature with adequate capacity. In the dog, blood supply to the brain arises from the basilar and internal carotid arteries, which join at the base to form the arterial circle of Willis. The cerebrum is supplied by three pairs of cerebral arteries arising from this arterial circle, with each one responsible for the perfusion of large but overlapping areas of the cerebrum. Any diseases which affect the cerebral blood vessels will cause disturbances of the cerebral blood flow (CBF) which in turn can lead to tissue damage. The metabolism of the brain is solely aerobic and without any significant energy reserves. The exceptionally high demand for circulating blood and oxygen is reflected is reflected in the disproportionately high rate of CBF compared with flow to other parts of the body, comprising 20% of the cardiac output and 15% of oxygen consumption when the body is at rest, even though the brain makes up only 2% of the body weight.

Cerebral ischemia is the reduction, although not necessarily the cessation, of blood flow to a level incompatible with normal function; the impairment may be global or regional. Ischemia, viewed simplistically as hypoxia plus hypoglycemia, will affect the most sensitive elements in the tissue, and if severe, persistent, or both, perturb all components. In its mildest form, impaired regional CBF causes a transient ischemic attack (TIA). TIA has an abrupt onset but is a rapidly diminishing neurological deficit of vascular origin, which lasts for less than 24 hours. This is well documented in humans but has not been studied in dogs, although the author believes that this occurs in dogs, occasionally as a historical precursor to an infarction.

Severe ischemia, which in the CNS would produce necrosis of the neurons and glial elements, results in an area of dead tissue termed an *infarct*. Severe arterial hypotension produces bilateral infarction in the boundary or watershed zones between major arterial territories. The critical threshold values of CBF needed for the maintenance of functional and structural integrity of the brain has been determined to be approximately 40% of the normal value (ie, approx. 20 mL/100 g/ minute). From about 40% to 30%, increasing numbers of neurons are unable to produce sufficient energy to maintain the functions needed for the transmission of nerve impulses, and at about 30% of normal blood flow transmission ceases completely although the cells can stay alive, as in a TIA. If regional CBF further diminishes below about 15% of normal (10–12 mL/100 g/minute), there is absolute membrane failure resulting in an irreversible nerve cell injury, as in an infarct. These levels can be higher in an already compromised brain.

In humans, there are regions of vulnerability within the brain where neurons are prone to be injured by global hypoxia-ischemia and hypoxia. These areas are the cerebral cortex, the hippocampus, the amygdala, several basal and thalamic nuclei, and the cerebellar cortical purkinje cells.

Infarction can result from arterial obstruction or venous thrombosis; arterial infarction can be due to either obstruction from thrombosis or embolism or to occlusion from blood vessel abnormalities such as vasculitis. A number of classification systems for ischemic stroke have been proposed in humans. The most commonly used clinical systems divide ischemic stroke into three major stroke subtypes: large artery or atherosclerotic infarctions, cardioembolic infarctions and small vessel or lacunar infarctions. Atherosclerotic infarctions are the most common subtype documented in people. Although the frequency of the three different subtypes is as yet unknown in dogs, atherosclerosis has been reported in dogs; it is especially seen in older dogs, dogs with hypothyroidism, and Miniature Schnauzers with idiopathic hyperlipoproteinemia. Other diseases associated with infarction in dogs include sepsis, coagulopathy, neoplasia and heartworm infections. The use of MR with techniques such as diffusion-weighted imaging and angiography may well help to define the subtype of infarction in the future. Because of abundant venous anastomoses, venous infarction is uncommon in dogs; as arterial blood flow is preserved, hemorrhage and edema tend to be more severe in venous infarction than in arterial infarction.

Cerebrovascular accidents can on occasion result from hemorrhage. This can occur within or around the brain and may result in rapid cerebral dysfunction often by alteration in cerebral volume (mass effect). It is classified as epidural, subdural, subarachnoid, intraparenchymal (primary or secondary), or intraventricular. When the bleeding is substantial enough to form an excessive additional volume within the CNS, the results can be fatal. The presence of a hematoma initiates edema and neuronal damage in surrounding parenchyma. Fluid begins to collect immediately in the region around the hematoma, and edema usually persists for up to 5 days, and in some cases as long as 2 weeks. Early edema around the hematoma results from the release and accumulation of osmotically active serum proteins from the clot. Vasogenic edema and cytotoxic edema subsequently follow owing to the disruption of the blood–brain barrier, the failure of the sodium pump, and the death of neurons. The delay in the breakdown of the blood–brain barrier and the development of cerebral edema after intracerebral hemorrhage suggest that there may be secondary mediators of both neural injury and edema. It had been thought that cerebral ischemia occurred as a result of mechanical compression in the region surrounding the hematoma, but recent studies in animals and humans have not confirmed this. It is currently thought that blood and plasma products mediate most secondary processes that are initiated after an intracerebral hemorrhage. Neuronal death in the region around the hematoma is predominantly necrotic, with recent evidence also suggesting the presence of programmed cell death (apoptosis).

The source of primary intraparenchymal hemorrhage is incompletely understood but human patients often have systemic hypertension with concurrent fibrinoid degeneration of arteries in the brain. Hypertension in dogs may be primary or secondary to disorders such as renal disease, and hyperadrenocorticism; these animals may be predisposed to intracranial hemorrhage. A variety of secondary causes of hemorrhage exist in dogs. Dogs with brain infarction can have associated hemorrhage, as can dogs with intracranial tumors, vasculitis or coagulopathies.

CLINICAL SIGNS

CVA are characterized clinically by a peracute or acute onset of focal, asymmetrical and nonprogressive brain dysfunction. Worsening of edema (associated with secondary injury phenomenon) can result in progression of neurological signs for a short period of 24 to 72 hours. Hemorrhage may be an exception to this description and be presented with a more progressive onset. Clinical signs usually regress after 24 to 72 hours; this is attributable to diminution of the mass effect secondary to hemorrhage and reorganization or edema resorption. With brainstem involvement, neurological examination of the cranial nerves will define the exact location and extension of the lesion. With forebrain lesion, the clinical sign may vary from simple disorientation to death. A unilateral lesion will induce ipsilateral circling, hemi-inattention syndrome, contralateral central blindness, as well as contralateral ataxia and proprioception deficits. Seizures are reported to be very common in association with CVA in dogs.

DIAGNOSIS

Blood and urine analysis is indicated to identify the possible underlying causes described above. Thyroid function (FT_4, TT_4 and endogenous cTSH levels), a coagulation profile (including a buccal mucosal bleeding time, a prothrombin time, a partial thromboplastin time and fibrinogen degradation products), and if possible multiple systolic blood pressures and an ECG, should be evaluated in any animal suspected of CVA. A fecal analysis should be performed to rule out parasitic infestation. Blood and urine cultures are indicated in case of sepsis. Cerebrospinal fluid analysis is unlikely to confirm a diagnosis of CVA but may help to rule out inflammatory CNS disease or may on occasion reveal recent hemorrhage (xanthochromia), normal to increased protein and a mild neutrophilic or mononuclear pleocytosis. Imaging studies of the brain (computed tomography {CT} or magnetic resonance imaging {MRI}) are necessary to confirm the clinical neurolocalization, re-enforce the suspicion of CVA, identify associated mass effect and rule out other causes of focal brain disorders (trauma, tumor, inflammation). CT also allows rapid image acquisition, in addition to the fact that changes associated with ischemia/infarction can be detected as early as 3 to 6 hours after the onset. Enhancement usually appears after 24 to 48 hours and is most evident after 1 or 2 weeks especially in the periphery where neovascularistion exists.

MR imaging is more sensitive than is CT in early infarction, with changes seen within an hour if onset. Magnetic resonance imaging is more sensitive in the detection of edema, provides multiplanar views, and lacks beam-hardening artifact when compared with CT. The conventional imaging findings in evolving cerebral infarction are well characterized and follow a temporal evolution similar in many ways to that seen on CT. These changes seen in ischemic parenchyma rely on an increase in tissue water content. Gradually, during the acute stage, the T2-weighted image becomes more hyperintense in the ischemic region, particularly over the first 24 hours. These signal changes seen in the first 24 hours are best appreciated in grey matter and are well visualized in deep gray matter structures such as the thalamus or basal ganglia, in addition to cortical gray matter. Gadolinium enhances infarcts because of vascular rupture but does not enhance ischemia or edema.

Computed tomography is very sensitive for acute hemorrhage, with a linear relationship demonstrated between CT attenuation and hematocrit. In a patient with a normal hematocrit, acute hemorrhage is seen as an area of increased attenuation, which tends to increase for the first 72 hours and then slowly decreases to isodensity at about 1 month post hemorrhage. The periphery of the lesion may enhance from approximately 6 days to 6 weeks after onset, on a CT scan.

The initial MRI appearance of hemorrhage is dependent on the age of the hematoma, among other determinants, which determines its unique signal intensity patterns. Localization of hemorrhage to the parenchyma or "extra-axial" space is central to assessing the etiology and the initiation of treatment. In dogs, it is more common to see intraparenchymal than "extra-axial" hemorrhage, the latter of which is typically subdural in location.

Other imaging modalities which may be utilized to investigate CVAs include cerebral angiography, to demonstrate vascular malformations; cerebral scintigraphy as a nonspecific way to identify a brain lesion; Doppler ultrasonography to analyze cerebral blood flow; and single photon emission computed tomography (SPECT) to analyze regional blood flow. These modalities are not frequently used now as the advances possible with MR technology mean that blood vessel abnormalities and regional blood flow can be assessed in conjunction with the structural abnormalities suggestive of a CVA.

TREATMENT

Ischemic Stroke

Treatment of an ischemic stroke revolves around three principles:

(1) Monitoring and correction of basic physiologic variables (eg, oxygen level, fluid balance, blood pressure, body temperature)
(2) Inhibition of the biochemical and metabolic cascades subsequent to ischemia to prevent neuronal death (concept of neuroprotection)
(3) Restoration or improvement of cerebral blood flow by thrombolysis in the presence of a thrombus.

The potentially salvageable portion of the ischemic zone (ischemic penumbra) is the presumed therapeutic target for both thrombolytic and neuroprotective stroke therapy. The time period during which injury may be reversible is called the *therapeutic window*. It is estimated that this "window of opportunity" is approximately 6 hours before the irreversible neurological damage occurs. Fortunately, the vast majority of ischemic stroke patients have no major difficulty maintaining their airways, breathing efforts or circulatory competence early in their clinical course.

Some controversies exist surrounding the management of hypertension in the setting of an ongoing acute ischemic stroke. As well as being a potential risk factor, hypertension can occur as a physiological response to a stroke to ensure an adequate cerebral perfusion pressure in the penumbra of the infarct for up to 72 hours after the onset. Maintenance of systemic arterial blood pressure within the physiological range is essential and aggressive lowering of blood pressure should be avoided during the acute stages unless the patient is at a high risk of end-stage organ damage (systolic blood pressures remaining above 180 mmHg). In such cases, hypertension can often be controlled with an angiotensin converting enzyme (ACE) inhibitor such as enalapril (0.25 to 0.5 mg/kg BID) or benazepril (0.25 to 0.5 mg/kg bid) and/or calcium channel blockers such as amlodipine (0.1 to 0.25 mg/kg SID) which tends to be more effective. There is no evidence that glucocorticoid treatment provides any beneficial neuroprotection in stroke. Aside from the lack of proven benefit in veterinary stroke patients, the use of glucocorticoids may increase the risk of gastrointestinal complications and infection. Treatment strategies for ischemic stroke considered in humans utilizing other neuroprotective agents (*N*-methyl-D-aspartate [NMDA] antagonists, Ca^{2+} channel blockers, sodium channel modulators) or anti-platelets and thrombolytic therapy remain to be evaluated clinically in dogs. Although the above neuroprotective agents have resulted in a dramatic decrease in the size of stroke lesion in experimental animal models, these agents have either failed to prove their efficacy in clinical trials or are awaiting further investigation. At the time of writing, there is no definitive data in humans or animals to confirm a significant improvement in clinical outcome in patients with acute ischemic stroke treated with unfractionated heparin as thrombolytic therapy. Despite conflicting results regarding its efficacy, intravenous recombinant tissue plasminogen activator (tPA) is sometimes used in human stroke patients if it can be given within the first 3 hours. This critical time window makes the use of thrombolytic treatment unrealistic in veterinary neurology. Furthermore, this type of treatment carries a significant risk of intracranial hemorrhage following treatment. Antiplatelet therapy with low-dose aspirin (0.5 mg/kg PO SID) can be used prophylactically to prevent clot formation in proven cardiac sources of an embolus.

Hemorrhagic Stroke

The medical management of dogs with intracranial hemorrhage commonly includes stabilization of the patient (airway protection, monitoring and correction of vital signs); assessment and monitoring of the neurological status; determination and treatment of potential underlying causes of the hemorrhage; assessment for the need for specific treatment measures including management of raised intracranial pressure (ICP).

The risk of neurological deterioration and cardiovascular instability is highest during the first 24 hours after the onset of an intracranial hemorrhage, as the space-occupying lesion slowly expands and cerebral vasogenic edema develops. Careful monitoring including assessment of vital parameters (eg, oxygen levels, fluid balance, blood pressure, body temperature) as well as neurological status, is therefore essential during this initial period. Unfortunately, clinical signs of raised intracranial pressure are often delayed, inconsistent and non-specific. The size of an intracranial hematoma can be difficult to estimate from the neurological examination alone. Intracranial pressure monitoring systems are frequently employed in human hospitals but their use is far from being widespread in veterinary hospitals. As a hematoma develops initially, ICP may be maintained at a constant due to a system of compensation. Within the closed space of the skull, a change in the volume of one intracranial constituent (brain tissue, arterial blood, venous blood and CSF) will be balanced by a compensatory change in another being incompressible. This is the Monroe-Kellie doctrine, which explains why some animals with large intracranial bleeds may develop substantial increases in ICP at the time of herniation. The exhaustion of the compensating mechanisms for an intracranial space occupying lesion implies that any further increase in the volume of the hematoma will produce a massive rise in ICP and clinically this can be associated with herniation. Due to mechanical autoregulation, cerebral blood flow (CBF) remains constant even though the cerebral perfusion pressure (CPP) may vary between 40 and 120 mmHg. The normal autoregulation of CBF may be impaired following cerebrovascular accidents, causing blood flow to damaged regions to become directly dependent on systemic blood pressure. Such animals may be unable to compensate for reductions in mean arterial blood pressure (MABP), causing decreased CPP in the presence of increased ICP. This emphasizes the importance of maintaining systemic blood pressure. In these circumstances, systemic hypotension can result in inadequate perfusion of the brain which leads to cerebral ischemic and secondary neuronal injury. Hypovolemia should be recognized and treated with volume expansion using crystalloids, colloids or hypertonic saline. Central venous pressure monitoring is very useful as an aid to assessing the effectiveness of resuscitation. The use of glucose-containing solutions is discouraged as hyperglycemia has been shown to correlate with poor outcome in human stroke patient. As such blood glucose should be monitored from the time of presentation. However, moderate levels of hypertension should not be treated as systemic hypertension may be secondary to the intense reflex sympathetic response to intracranial hypertension which is a compensatory mechanism to maintain cerebral perfusion. As for ischemic stroke, attempts to lower and normalize the blood pressure should be reserved for animals at a high risk of end-stage organ damage (systolic blood pressures remaining above 180 mmHg) and/or animals with severe ocular manifestations of hypertension such as retinal detachment or intraocular hemorrhage. Treatment recommendations for lowering blood pressure are detailed in the above section on treatment of ischemic stroke.

There is no evidence in humans to support the routine use of oxygen for the treatment of hemorrhagic stroke, in the absence of hypoxia. In a rapidly deteriorating animal, hyperventilation can temporarily be used to reduce ICP. The aim of hyperventilation is to reduce cerebral blood volume and hence ICP, by causing a hypocapnic vasoconstriction. However excessive hyperventilation can be accompanied by a reduction in global cerebral blood flow, which may drop below ischemic thresholds, therefore it is not a recommended therapy unless the $PaCO_2$ can be closely monitored with capnography or arterial blood gas analysis.

Mannitol has traditionally been used to treat intracranial hypertension associated with pathologies such as head trauma, brain tumors, or encephalitis. There is insubstantial evidence to suggest that mannitol exacerbates intracranial hemorrhage; therefore osmotic diuretics are routinely used in the control of ICP in human patients with known intracranial hemorrhage. Mannitol therapy (0.25–1.0 g/kg IV over 10 to 20 minutes up to q8h) may be initiated to treat suspected elevated ICP secondary to hemorrhagic stroke. Mannitol's main effect is to enhance cerebral blood flow by reducing blood viscosity. Surgical evacuation of the hematoma can be employed in dogs with large hematomas (mostly subarachnoid) and a deteriorating neurological status.

PROGNOSIS

The prognosis for ischemic or hemorrhagic stroke depends oveall on the initial severity of the neurological deficit, the initial response to supportive care, and the severity of the underlying cause if one has been identified. Fortunately, most cases of ischemic stroke recover within several weeks with only supportive care. In a recent retrospective study of 33 dogs with MRI or necropsy evidence of brain infarction, there was no association between the region of the brain involved (telencephalic, thalamic/midbrain, cerebellum), the type of infarction (territorial or lacunar), and the outcome. However, dogs with a concurrent medical condition had a significantly shorter survival time than those dogs with no identifiable medical condition. Dogs with a concurrent medical condition also were significantly more likely to suffer from recurrent neurological signs due to subsequent infarcts.

INFLAMMATION OF THE CNS – IS THERE EVIDENCE FOR THE MEDICINE?

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The hallmark of central nervous system (CNS) inflammation is infiltration of peripheral blood leukocytes into the neuroparenchyma and its coverings, resulting in various types of encephalitis and/or meningitis, and sometimes associated with altered vascular integrity that leads to edema. The etiologies of inflammatory disease of the CNS are very diverse. Simplistically, they can be classed as pathogenic and non-pathogenic, with the latter being potentially related to immune-system dysfunction. Infectious causes may be viral, protozoal, bacterial, rickettsial, or fungal.

GRANULOMATOUS MENINGOENCEPHALOMYELITIS

Granulomatous meningoencephalomyelitis (GME) is a sporadic, idiopathic, inflammatory disease of the CNS of dogs. This disease appears to have a worldwide distribution, with recent reports coming from the US, Australia, New Zealand, and Europe. The cause of GME is unknown.

Most cases of GME occur in small-breed dogs, and commonly in terrier and toy breeds and Poodles, although any breed may be affected. The majority of confirmed cases occur in young to middle-aged dogs, with a mean age around 5 years (ranging from 6 months to 12 years). GME occurs in both sexes; however, there appears to be a higher prevalence in females. A lack of obvious correlation between clinical signs and the course of the disease has been reported. Clinical signs usually reflect several (ie, multifocal) syndromes, eg, cerebral, brain stem, and spinal cord syndromes, as a result of the scattered distribution of lesions. However, focal signs have been reported in up to 50% of cases. Common signs include incoordination, ataxia and falling, cervical hyperesthesia, head tilt, nystagmus, facial and/or trigeminal nerve paralysis, circling, visual deficits, seizures, depression, and tetanic spasms. Occasionally, fever, peripheral neutrophilia, and excess non-segmented neutrophils will accompany the clinical neurological signs. An infrequently reported ocular form of GME appears to be related to lesions localized in optic nerves and optic chiasm resulting in visual impairment and abnormal pupillary reflexes.

A tentative diagnosis of GME may be suggested by signalment data, the clinical course of the disease, and clinical signs. Hematology, serum chemistry, and urinalysis studies are usually normal and electroencephalographic recordings are frequently non-specific. Rarely, an intrathecal filling defect may be detected myelographically in dogs possibly due to focal cord swelling or subarachnoid granulomas. The most useful diagnostic aid is cerebrospinal fluid (CSF) analysis. In most dogs, CSF is abnormal with mild to pronounced pleocytosis, ranging from 50 to 900 WBCs/μL. Cells are predominantly mononuclear, including lymphocytes (60– 90%), monocytes (10–20%), and variable numbers of large anaplastic mononuclear cells with abundant lacy cytoplasm. While neutrophils typically comprise from 1% to 20% of the cell type differential, they may be the predominant cell type on rare occasions. Occasionally, protein is elevated without pleocytosis. In one retrospective study of dogs with GME, lumbar-derived CSF contained fewer cells and less protein than CSF derived from cisternal puncture. CSF protein and cellularity is not necessarily influenced by the degree of meningeal involvement or the extent of necrosis within the granulomatous lesions. A combination of CSF and MRI findings may also be useful, the latter being characterized by isointense lesions on T1-weighted images. Pial/dural meningeal enhancement may be found with MRI. Although infrequently performed, brain biopsy can be a very useful diagnostic test in animals with focal lesions.

Prognosis for permanent recovery is guarded. Some dogs die from inhalation pneumonia secondary to megaesophagus. Shortest survival periods, ranging from several days to weeks, are seen with the disseminated and ocular forms. Longer survival periods of from 3 to 6 months, or longer, are more suggestive of a focal lesion. In one retrospective study of 42 dogs with GME, median survival time for dogs with focal versus disseminated disease was 114 and 14 days, respectively, and dogs with focal forebrain signs (eg, seizures) had significantly longer survival times (>395 days) than did dogs with focal signs in other areas of the CNS (59 days).

Long-term therapy is generally unsatisfactory, although temporary remission of signs is often achieved with corticosteroid administration, such as oral prednisone, 1 to 2 mg/kg/day initially for several days, then reducing the dosage to 2.5 to 5 mg on alternate days. Most dogs will require continued therapy to prevent recurrences of signs. Improvement may last for several days, weeks or months, although most will eventually succumb to the disease. Part of the temporary improvement may be related to a reduction of mast cell function in dogs receiving glucocorticoid medication. Cessation of glucocorticoid therapy is invariably associated with rapid and dramatic clinical deterioration. Results of a recent retrospective study suggested that radiation therapy (eg, total doses ranging from 40 to 49.5 Gy, divided in 2.4- to 4.0-Gy fractions) may be an effective treatment for dogs with GME, particularly those with clinical signs suggesting focal involvement. Promising clinical results following use of cytosine arabinoside (at 50 mg/m^2, SQ, bid x 2 days, repeat every 3 weeks) suggests that this potent anti-inflammatory drug may be an effective sole therapy for the long-term treatment of GME in dogs. Other immunosuppressive treatment options include mycophenolate, leflunomide, cyclosporine, cyclophosphamide, and azathioprine.

STEROID-RESPONSIVE MENINGITIS-ARTERITIS

A severe form of steroid-responsive meningitis-arteritis (SRMA) has been reported in Beagles, Bernese Mountain Dogs, Boxers, German Short-Haired Pointers, and sporadically in other breeds. This condition has a worldwide distribution and represents one of the most important inflammatory diseases of the canine CNS. Beagles, especially but not exclusively those in laboratory-bred colonies, appear at risk. In Beagles, the condition has been termed *Beagle pain syndrome, necrotizing vasculitis, polyarteritis, panarteritis, juvenile polyarteritis syndrome,* and *primary periarteritis.* In other breeds, this condition previously appears under the terms *necrotizing vasculitis, corticosteroid-responsive meningitis, aseptic suppurative meningitis,* and *corticosteroid-responsive meningomyelitis*. This plethora of terminology reflects not only the dearth of knowledge about this condition but also highlights important clinical signs such as pain, improvement following corticosteroid medication, and histologic involvement of the meninges and blood vessels.

Affected animals usually are most commonly young adults between 8 and 18 months of age, although the age range may extend from 4 months to 7 years. The clinical course is typically acute with recurrences. A more protracted form of the disease may be seen following relapses and inadequate treatment. Signs include recurring fever, hyperesthesia, cervical rigidity, and anorexia. There may be a creeping gait, arching of the back with head held down, and crouched posture. Some dogs with protracted disease may show clinical signs of parenchymal involvement such as ataxia, paresis, tetraparesis or paraplegia. Hematological studies often reveal a peripheral neutrophilia with a left shift, increased erythrocyte sedimentation rate, and in some cases, an elevated α2-globulin fraction. CSF studies indicate increased protein and neutrophilic pleocytosis.

The cause of SRMA remains unknown. To date, no bacterial or viral infectious agents have been identified, although activated T cells have been found in some dogs indicating these cells have had contact with some unidentified antigen.

The prognosis is guarded to favorable, especially in dogs with acute disease that are treated promptly using immunosuppressive doses of corticosteroids. Untreated dogs tend to have a remitting and relapsing course. Tipold recommends the following long-term therapy (eg, for at least 6 months), especially in any dog that has had a relapse: prednisolone at 4 mg/kg/day, PO or IV initially. After 2 days, the dose is reduced to 2 mg/kg daily for 1 to 2 weeks, followed by 1 mg/kg daily. Dogs are re-examined, including CSF analysis and hematology, every 4 to 6 weeks. When signs and CSF are normal, the dose can be reduced to half of the previous dosage until a dosage of 0.5 mg/kg every 48 to 72 hours is attained. Treatment is stopped 6 months after clinical examination, CSF, and blood profiles are normal. In refractory cases, other immunosuppressive drugs such as azathioprine (at 1.5 mg/kg PO every 48 hours) may be used in combination with steroids (eg, alternating each drug every other day). Antibiotics are ineffective. Results of a long-term treatment protocol (up to 20 months) involving 10 dogs with SRMA have been recently published. Eight of the 10 dogs were without clinical signs up to 29 months after the treatment was terminated. Long-term glucocorticosteroid treatment resulted only in mild clinical side effects, such as polyuria/polydipsia, polyphagia and weight gain, which were reversible after the therapy was discontinued. It was noted that elevated serum and CSF IgA levels did not decrease to normal values during prednisolone treatment and were still slightly increased after the therapy was discontinued. Monitoring of CSF cell count in dogs with this condition was a sensitive indicator of success of treatment. In addition, older dogs with high IgA levels in the CSF and frequent relapses seemed to require a longer duration of therapy and had a less favorable prognosis long term.

Note that Akitas, Bernese Mountain dogs, and other breeds with immune-mediated polyarthritis may show similar clinical signs as animals with SRMA and have concurrent meningitis.

BACTERIAL MENINGITIS

Bacterial meningitis is a rarely reported condition in dogs and cats. Animals of any age may be affected, although most affected dogs are adult, with a mean age around 5 years. Bacterial infections of the CNS most often occur via hematogenous spread from distant foci within the body (eg, lung or splenic abscess, vegetative endocarditis, pleuritis, and urinary tract infections), by direct extension from sinuses, ears and eyes, as a result of trauma (eg, bite wound), meningeal spread with entry along nerve roots, or from contaminated surgical instruments (eg, spinal needle). Organisms usually disseminate via CSF pathways and produce cerebrospinal meningitis, often associated with microabscess formation of brain and spinal cord. A plethora of organisms have been cultured from dogs with bacterial meningitis including *Pasteurella* sp (eg, *P. multocida*), *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Staphylococcus albus*, *Actinomyces* sp, *Nocardia* sp, *Escherichia coli*, *Streptococcus* sp (eg, *S. pneumoniae*) and *Klebsiella* sp.

Irrespective of the etiologic agent, bacterial meningitis usually is acute in onset and tends to be characterized by a group of clinical signs that include hyperesthesia, fever, cervical pain, and frequently, cervical rigidity. In addition, vomiting, bradycardia, anorexia, occasional cranial nerve deficits, and seizures may be observed. Seizures may be caused by high fever, hypoglycemia, brain edema, or inflammation, while vomiting may result from increased intracranial pressure or from direct effects on the vomiting center. In some animals, clinical signs may develop that suggest parenchymal involvement. The clinical diagnosis of bacterial meningitis is supported by the finding of highly pleocytic CSF (500 to 1000+ WBCs/μL) with a high proportion of neutrophil cells. The protein content of the CSF is usually increased as well (100 to 1000+ mg/dL. Low CSF glucose, relative to plasma glucose values, are typical. Organisms may be seen on CSF cytology. Neutrophilia may be present in blood samples and there may be evidence of shock, hypotension, and disseminated intravascular coagulation Thrombocytopenia, abnormal liver enzymes, electrolyte imbalance, abnormal anion gap, and uremia have been reported in some cases. Electroencephalographic traces may demonstrate high voltage (30– 70 μV), fast (20–35 Hz) or slow (5– 10 Hz) wave activity. Definitive diagnosis is made by bacterial culture of CSF (both aerobic and anaerobic). Blood and urine cultures may incriminate a pathogenic organism when CSF cultures are negative (which is usually the case in our experience). Meningeal inflammation, ventriculitis, and possibly brain edema can be detected using MRI or CT scans.

Prognosis is guarded since death is common even if appropriate therapy is administered, and relapses are frequently encountered. Appropriate use of antibiotics, according to the culture results, is basic to successful therapy of bacterial meningitis (encephalomyelitis). Antibiotic therapy should be maintained for several weeks after clinical signs have resolved. Chloramphenicol (up to 50 mg/kg, IV, IM, or SC, bid), metronidazole (10–15 mg/kg, PO, tid), trimethoprim-sulfonamide (from 30–60 mg/kg, PO, daily; note that complications may include sulfonamide urolithiasis in dogs and nephrotoxicity in cats) penetrate the CNS in therapeutic concentration. Ampicillin and penicillin enter the CNS only with meningeal irritation. Aminoglycosides and cephalosporins reportedly do not adequately penetrate the CNS, even when inflammation exists. Intrathecal administration of antibiotics should only be considered in refractory cases. Corticosteroids, in general, are contraindicated in the treatment of bacterial meningitis. It has been suggested that *Staphylococcus* sp. should be assumed when the organism involved is not known. Ampicillin, 5–10 mg/kg, IV, every 6 hours is recommended. Diazepam or other anticonvulsants can be used for seizures if they occur. Osmotic diuretics may be useful for treating increased intracranial pressure secondary to brain edema.

Note that it may be very difficult to differentiate between bacterial meningitis and steroid-responsive meningitis-arteritis (SRMA). The latter is more common and probably should be at the top of the differential list. Analysis of CSF for elevated levels of IgA should be diagnostic for SRMA.

MYCOTIC DISEASES OF THE CNS

Mycotic agents sporadically produce a granulomatous meningoencephalomyelitis in dogs and cats. The more common mycotic infections of the CNS are caused by *Cryptococcus neoformans*, *Blastomyces dermatitidis*, *Histoplasma capsulatum*, and *Coccidioides immitis*. Each agent has a particular geographic distribution in the US. The pathogenesis is similar for blastomycosis, histoplasmosis, and coccidioidomycosis. The organism is present in the soil, producing mycelia and airborne spores. The coccidia of spores are probably inhaled, deposited in the alveoli, phagocytosed and converted into the spherical parasitic, yeast form. This form is disseminated via lymphatics producing local hilar lymphadenopathy and there is hematogenous spread to other organs. The fate of the infected host is believed to be dependent upon time and ability to develop cellular immunity to fungal antigens. Unlike other mycotic diseases, *C. neoformans* exists only in the yeast form and has a worldwide distribution. Endemic areas have not been identified. Infection is probably acquired from the environment rather than from animals. Cryptococcosis infection often occurs in mature dogs and cats that are immunodepressed (eg, cats with feline leukemia virus or feline immunodeficiency virus, or dogs with ehrlichiosis), and infection may be accelerated or worsened by glucocorticoid therapy. Cats contract the disease more frequently than dogs. The natural route of infection is generally believed to be the respiratory tract, with subsequent hematogenous and lymphogenous dissemination to other areas of the body. As with bacteria, mycotic infections also may reach brain and spinal cord by direct spread from an adjacent infection, eg, from the nasal chambers, tooth alveolus and sinuses, outer ear, eustachian tube, middle/inner ear, petrous temporal bone, and basilar bone.

Pyogranulomatous encephalitis has been reported occasionally in dogs and cats in association with blastomycosis. Neurological disease associated with histoplasmosis and coccidioidomycosis is rare or quite uncommon, although granulomatous meningitis attributable to *C. immitis* was diagnosed on postmortem examination in a 4-year-old Border Collie by demonstration of *Coccidioides* endospores in brain tissue. There are a few reports of CNS infection in dogs and cats associated with uncommon opportunistic fungi, such as phaeohyphomycoses, in which the agents involved are almost always *Cladosporidium* species, and usually *C. bantianum*. CNS disease is usually due to localized brain abscess or to multiple large pyogranulomatous lesions in the cerebrum and meninges, sometimes with multifocal malacic foci, and is invariably fatal.

Diagnosis of mycotic infection is based on demonstration of the organisms in tissue sections using immunofluorescent procedures or in material taken from aspirates or impression smears, culture, and serology. A commercial latex agglutination test is available for detecting cryptococcal capsular antigen in serum, urine, or cerebrospinal fluid. Inflammatory mycotic lesions may be detected using MRI.

Prognosis of mycotic infection is always guarded, especially in the disseminated form and with CNS involvement. Most of the organisms are sensitive to treatment with amphotericin B (AMB), eg, using a dosage of 0.1 to 0.5 mg/kg body weight, IV, three times weekly, in dogs and cats. The treatment of choice for cryptococcosis still appears to be AMB and flucytosine (FCY), although toxic epidermal necrolysis may sometimes be seen as a side effect. A recommended dosage for FCY is 120 mg/kg body weight, divided into four equal doses daily. Due to the inability of AMB and FCY to cross the blood–CNS barrier, it is recommended that these drugs be used in combination with other antifungal agents such as itraconazole (ITZ, at 5–10 mg/kg, PO, bid) or fluconazole (FCZ, at 5–15 mg/kg, PO, bid) in animals with CNS disease. It would seem that the same recommendation would apply to other fungal diseases having CNS involvement, eg, itraconazole at 10 mg/kg, PO, daily is suggested for dogs with blastomycosis/brain involvement. In a recent report of cryptococcosis in 19 cats, treatment with ketoconazole (KTZ), was unrewarding in cases with CNS involvement, although KTZ and ITZ (both at 10 mg/kg, PO, daily) successfully treated a small number of experimentally infected cats, including some with CNS disease.

PROTOZOAN ENCEPHALITIS-ENCEPHALOMYELITIS: TOXOPLASMOSIS AND NEOSPOROSIS (TX-NS)

Toxoplasmosis is an infectious condition caused by the protozoal parasite *Toxoplasma gondii* and occurs in acquired and congenital forms in man and animals. Cats are the definitive host for this parasite. TX-NS in dogs resulting in a systemic infection will typically affect most organs, and the CNS, in particular. Neurological signs associated with TX-NS encephalomyelitis are variable and may reflect a focal or multifocal disease process. In dogs, signs include hyperexcitability, depression, intention tremor, paresis, paralysis, head tilt, and seizures.

In the diagnosis of TX-NS neurological disease, abnormal hematological parameters may include non-regenerative anemia, neutrophilic leukocytosis, lymphocyosis, and eosinophilia. Serum alanine aminotransferase and aspartate aminotransferase levels may be increased, especially in dogs with acute hepatic and muscle necrosis. Results of CSF may be abnormal, with elevated protein content and a mixed monocytic-polymorphonuclear pleocytosis. An eosinophilic pleocytosis was found in two dogs with a granulomatous encephalomyelitis due to protozoan infection. Xanthochromia will be present if hemorrhage has occurred. Electromyographic testing may reveal fibrillation potentials, positive sharp waves, bizarre high-frequency potentials, and myotonic-like discharges. Nerve conduction velocities may be decreased. Serum creatine kinase levels are often increased. Protozoan meningoencephalitis has been detected using MRI scans. The close resemblance between *T. gondii* and *N. caninum* tachyzoites and tissue cysts prevents definitive diagnosis by histopathology, and the clinical syndromes appear to be identical. Differentiation between the two protozoan organisms can be made using assays for circulating antibodies, by tissue immunocytochemistry, and ultrastructural studies. Sensitive polymerase chain reaction assays have been reported for the detection of both *Neospora caninum* DNA and *Toxoplasma gondii* DNA in biological samples. Muscle biopsy of appropriate muscles (as suggested by the clinical signs) may also provide the possibility of a definitive premortem diagnosis using the aforementioned techniques.

Prognosis is poor when signs of pelvic limb spasticity are observed and is guarded in any animal with signs of CNS disease. In one study involving 27 cases of neosporosis, recovery was less likely in peracute cases with severe clinical signs, and when treatment was delayed. Many animals with myositis-polyradiculoneuritis have concomitant lesions in the CNS. A 4- to 8-week regimen of trimethoprim-sulfonamide (at 15–20 mg/kg combined dose, PO, bid) and pyrimethamine (at 1 mg/kg, PO, daily) has successfully treated animals with TX-NS–induced encephalomyelitis and myositis-polyradiculoneuritis. Clindamycin is considered to be the drug of choice for treating canine and feline toxoplasmosis, at a dose of 10 to 40 mg/kg/day, PO or IM, divided bid to tid. This dose can also be used for treating dogs with neosporosis. Clindamycin crosses the blood–brain barrier. Oral and parenteral dosages are similar because of the good intestinal absorption of clindamycin. Oral clindamycin can cause anorexia, vomiting, or diarrhea in dogs and cats.

LUMBOSACRAL PAIN — TO CUT IS TO CURE?

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Lumbosacral pain in dogs has multiple etiologies. Pathological abnormalities of the lumbosacral region have been termed *cauda equina syndrome, lumbosacral stenosis, degenerative lumbosacral stenosis, lumbosacral spondylopathy, spondylolisthesis, lumbosacral malformation-malarticulation,* and *lumbosacral disease. Lumbosacral disease* is a collective term for a variety of pathological conditions that may include malformation, growth abnormalities, degeneration, compression, inflammation, infection, displacement and reduced vascular circulation. These conditions may involve the last lumbar vertebra, the sacrum, the lumbosacral disk, the soft tissue structures around the lumbosacral joint or the cauda equina and associated nerve roots. The most common cause of lumbosacral disease is degenerative lumbosacral stenosis. Lumbosacral instability, including dorsal dislocation of L7, has also been reported. Morphometric studies suggest that multilevel congenital or developmental stenosis of the lumbosacral canal may contribute to acquired lumbosacral stenosis in large-breed dogs. Other causes of acquired stenosis include diskospondylitis, neoplasia, and traumatic fracture/ luxation of L7–S1, sacrum, or the sacrococcygeal junction. Also, lumbosacral osteochondrosis, a developmental disturbance of the end plate of either the sacrum or L7 vertebra, with subsequent separation of an osteochondral flap, has been reported as a cause of lumbosacral stenosis in mature dogs

Diagnosis of this condition can be difficult especially when considering there may be a need to identify a surgically correctable lesion with a high degree of confidence.

CLINICAL SIGNS OF LUMBOSACRAL DISEASE

Lesions involving spinal cord segments L4–5 through S1–3 (+ coccygeal segments) or lumbosacral nerve roots that form the cauda equina (including femoral, obturator, sciatic, pudendal, pelvic, and coccygeal nerves) will result in a lumbosacral syndrome. The lumbosacral syndrome reflects various degrees of involvement of the pelvic limbs, bladder, anal sphincter, and tail. Clinical signs will range from flaccid weakness to paralysis of pelvic limbs and tail. Owners often note that affected dogs have difficulty rising or climbing stairs, and show signs of pain or stiffness during extensive physical activity. Clinical signs may include pain (the most commonly reported sign) during direct palpation (especially downward pressure) of the lumbosacral area or during lumbosacral hyperextension, unilateral or bilateral pelvic limb paresis or lameness, proprioceptive deficits, tail paresis, hypotonia of anal sphincter with faecal incontinence, and urinary incontinence. Patellar and withdrawal reflexes (as well as gastrocnemius and cranial tibial reflexes) may be depressed or absent in pelvic limbs, as may be perineal (anal) and bulbocavernosus (in male dogs) reflexes. Tone in pelvic limb muscles may be reduced or absent. After 1 to 2 weeks of clinical signs, segmental muscle atrophy due to denervation will be observed. "Segmental" refers to the particular spinal cord segment involved in the lesion (eg, segmental atrophy may develop in the iliopsoas, quadriceps, and sartorius muscles following an injury to the L4–6 spinal cord segments). Pain perception in pelvic limbs, tail, and perineum may be reduced or absent. Pelvic limb postural reactions such as hopping and placing may be depressed. Thoracic limb function is unaffected.

Normal micturition requires synchronized contraction of the urethral smooth muscle and relaxation of the urethral skeletal muscle. Urethral smooth muscle is supplied by pelvic (parasympathetic) and hypogastric (sympathetic) nerves; pelvic and hypogastric nerves form the pelvic plexus. The pudendal nerve innervates the urethral skeletal muscle. Lesions involving the pelvic nerves, sacral cord segments, or pathways to and from the brainstem will abolish the micturition reflex. Consequently, the bladder will distend with urine and eventually overflow. Lesions of the sacral segments will also result in loss of innervation to the skeletal muscle of the urethra. As a result of minimal urethral resistance, manual expression of the bladder is easy in such cases. Thus, animals with sacral cord lesions may suffer from continual overflow incontinence. The anal sphincter may be flaccid and dilated, resulting in faecal incontinence. Since the external anal sphincter is innervated by the pudendal nerve, which also originates in the sacral segments, the perineal (anal) reflex provides a good assessment of sacral spinal cord function.

In some animals with lumbosacral disk extrusion, one pelvic limb may be held in partial flexion or a repetitive "stamping" motion may be observed. These animals frequently show considerable pain on manipulation of the limb and lumbosacral spine. This combination of signs is termed "root signature" and is believed to be associated with nerve root compression or entrapment by a fragment of extruded disk material. The occurrence of exercise-induced pain in some affected dogs, termed *neurogenic intermittent claudication*, may be related to dilatation of radicular vessels and subsequent compression of adjacent nerve roots in a stenotic region, eg, intervertebral foramen or lateral recess of the caudal L7 vertebral foramen narrowed by a degenerative process.

SURVEY RADIOGRAPHY

On plain films, indirect evidence of degenerative lumbosacral stenosis includes spondylosis deformans, disk space narrowing, and end-plate sclerosis. None of these abnormalities are specific however, and they occur in clinically normal dogs. There may be evidence of lumbosacral fracture/luxation, osseous neoplasia, intradiscal osteomyelitis associated with discospondylitis, or congenital lumbosacral stenosis. However, the greatest limitation of survey radiography is the inability to assess compression of neural tissue. Survey radiographs need to be performed with the animal deeply sedated or under general anesthesia, properly positioned and preferably with an empty colon. In one study, over 30% of German Shepherds with clinical signs of cauda equina compression had radiographic abnormalities compatible with osteochondrosis of the sacral end plate. In another study, transitional vertebrae were found in nearly 40% of German Shepherds with degenerative lumbosacral stenosis and in 11% without. In dogs with lumbosacral osteochondrosis, a radiolucent defect occurs in the dorsal aspect of the affected end-plate along with one or more bone fragments in the vertebral canal and lipping, angling, and sclerosis of the dorsal part of the end-plates. Stress radiography, such as dynamic flexion/ extension studies, may accentuate the lumbosacral instability. One study evaluated the LS angle and degree of subluxation of the sacrum in relation to L7 as seen on survey radiographs in 52 normal dogs and 32 normal dogs with LS spondylosis (of which 24 had neurological deficits). The conclusion was that such measurements were not helpful in the diagnosis of this disease.

CONTRAST-ENHANCED RADIOGRAPHY

Epidurography and diskography may provide useful information. In one study, combined survey radiography and diskography-epidurography were correctly positive in 16 of 18 dogs (89%). Alone, epidurography has been reported to be diagnostic in 78% to 93% of dogs confirmed surgically. It is easier to perform than myelography and has less morbidity. The disadvantage is that filling of the epidural space may be incomplete because this space is poorly defined, contains fat and has multiple lateral openings. Flexed and extended views of the LS joint during epidirography may accentuate a compressive lesion. Concomitant filling of the vertebral venous sinuses or the paravertebral venous system may occur in normal dogs but is more common in those with LS disease.

Myelography has limited value in the evaluation of the cauda equina because the dural sac is elevated from the vertebral canal floor and often ends before the lumbosacral junction; It has been reported that 85% of normal dogs and 80% of dogs with degenerative lumbosacral stenosis had a dural sac that ended at the level of the sacrum and that myelography with the LS joint in neutral, flexed and extended positions was successful in the diagnosis of LS disease. In another study, 77% of 30 dogs had a dural sac that ended within the sacrum. Myelography allows evaluation of the spinal cord cranial to the LS region and thus may help to rule out other diseases.

Myelography performed at the cerebellomeduallry cistern produces less local artifact than does lumbar injection; lumbar myelography can be non-diagnostic when there is epidural leakage.

COMPUTED TOMOGRAPHY

Computed tomography and MRI are probably the diagnostic procedures of choice although findings of similar CT changes (but not vertebral subluxation) in the lumbosacral spine of older dogs without clinical disease may complicate diagnosis. Dorsal and sagittal images can be reformatted from the transverse ones. CT is accurate and allows evaluation of structures that cannot be visualised completely with conventional radiography such as the lateral recesses, intervertebral foramen and articular processes. It provides bone detail superior to that seen with MRI and soft tissue contrast superior to that of conventional radiography. It allows visualization of individual nerve roots because of the contrast provided by the epidural fat. Disadvantages of CT are the use of ionizing radiation and the cost and limited availability of this procedure.

In a study evaluating canine lumbosacral stenosis using intravenous contrast-enhanced CT, the positive predictive values for compressive soft tissues involving the dorsal canal, ventral canal and lateral recesses were 83%, 100%, and 81%, respectively. A gas-filled lumbosacral disk space (*vacuum disk* phenomenon) along with smaller gas bubbles in between the degenerated L5–L6 dorsal articular facets (*vacuum facet* phenomenon) has also been revealed by CT in a 7-year-old Rottweiler with cauda equina syndrome. A diagnostic role for CT densitometry awaits further studies

MAGNETIC RESONANCE IMAGING

MRI can clearly reveal soft tissue, such as cauda equina, epidural fat, and intervertebral disk, at the lumbosacral region without use of contrast medium. MRI is also considered to give better information about the condition of the intervertebral disk (eg, the hydration status of the nucleus pulposus) in dogs with degenerative lumbar spine diseases, than radiography or CT. However, no correlation was found between severity of the clinical signs and the severity of cauda equina compression as assessed by MRI in one study. In humans, it has been proposed that MR imaging can lead to over-diagnosis of disk disease because many people without back pain have disk bulges or protrusions on MR imaging. As MR imaging is used more frequently now in veterinary medicine, inconsistency between disk abnormalities and clinical signs must be considered, and the diagnosis should always be based upon clinical acumen in addition to the imaging.

ELECTROPHYSIOLOGY

Electromyographic (EMG) studies can demonstrate fibrillation potentials in lumbosacral paraspinal muscles, pelvic limbs, coccygeal muscles, and anal sphincter; as such this procedure can help confirm neurological disease as well as mapping out denervation. One study found that EMG was accurate in predicting the presence or absence of cauda equina compression in all cases. Another study found that some dogs with LS disease (particularly those presented with only pain) had normal findings on EMG, however. Dogs with mild disease can have a largely neurapraxic lesion that does not produce denervation.

TREATMENT

Medical

Confinement and anti-inflammatory medication may be successful in mild cases of degenerative lumbosacral stenosis with pain only. A long period of rest, of 3 to 4 months, can help improve at least 50% of dogs. However, the signs can recur and progress with time and such extended periods of inactivity are not practical for all cases, particularly working dogs. In addition to rest, medical management of discomfort should be addressed using anti-inflammatory steroidal therapy or nonsteroidal therapy. The use of gabapentin, a novel human anticonvulsant has been found to be successful in humans and dogs with nerve root pain when used at a dose of 10–20 mg/kg PO every 8 hours.

Surgical

Surgical treatment is indicated when nonsurgical management has failed; in working dogs, and in those with persistent pain or neurological deficits. It is unlikely that medical or conservative therapy is going to be effective in dogs with severe neurological deficits and or incontinence. These clinical signs can be permanent even following surgical therapy.

The choice of surgical procedure is often between dorsal laminectomy, distraction and fusion, or a combination of the two procedures. Definitive criteria for the choice of these procedures are currently contentious. A dorsal laminectomy alone is not effective for dogs with chronic incontinence based on a recent study. Fusion alone may be inadequate for dogs with neurological deficits and or severe pain. These presentations warrant combined dorsal laminectomy and fixation-fusion. Additional indications for distraction and fusion include a marked change in the degree of compression between flexion and extension or a "telescoping" of facets suggestive of instability. Foramenal decompression or facetectomy, which may require concurrent stabilisation, may be necessary for dogs with lateralised compression or foramenal stenosis.

Several studies have been published on the long-term prognosis after dorsal laminectomy. Two reported excellent or good results in 77% and 73% after average follow up periods of 14 and 21 months, respectively. Two larger and more recent studies reported mean follow-up mean follow up times of 26 and 38 months. In the first study of 131 dogs, 85% of the dogs with mild preoperative signs (no neurological deficits; mild pain; reluctance to jump and run) recovered to normal.; 79% of those dogs with moderate signs (moderate to severe pain; reluctance to exercise; proprioceptive deficits) recovered to normal; and 50% with severe signs recovered to normal. Overall, 79% of dogs became normal after surgery and 93% of dogs improved and outcome was independent of the preoperative duration of signs. Of the 131 dogs, 76 were active or working dogs and 78% of these returned to work. Nearly 20% of all dogs recurred with signs similar to presentation after a mean of 22 months. In the second study of 69 dogs, 78% had an excellent or good overall outcome with only 3% having a late recurrence of signs.

FELINE UPSIDE DOWN – VESTIBULAR DISEASE IN THE CAT

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The onset of a head tilt in cats is a cardinal sign of vestibular disease. It is the most consistent sign of unilateral vestibular dysfunction, which occurs as a result of the loss of anti-gravity muscle tone on one side of the neck. Bilateral vestibular disease may also cause a head tilt if the disease process is not symmetrical but usually does not cause such a sign. The vestibular system has two functional components; the peripheral component is located in the inner ear and the central component is located in the brain stem and cerebellum. Unfortunately, a head tilt is not specific for a brainstem or a peripheral vestibular system lesion localisation, nor does it indicate a specific etiology. Generally, central vestibular disease is associated with different etiologies and a worse prognosis than peripheral vestibular disease. Therefore, it is essential to approach these cases aiming to primarily further localize the neurological lesion.

DIAGNOSTIC PLAN

- Obtain a comprehensive history of the onset of the disease. Information regarding previous systemic disease, previous ear disease, previous medication administration (both topical and systemic), travel history, the possibility of toxin exposure and head trauma is important.
- Perform a complete neurological examination. There are several very important components of the examination that can assist with the lesion localisation. In addition to the head tilt, the other signs of vestibular disease include pathologic nystagmus, positional strabismus and ataxia characterized by a base-wide stance and swaying of the trunk and head. Pathological nystagmus can be spontaneous or positional. Spontaneous nystagmus is nystagmus that occurs when the head is not moving and is in the normal position. A unilateral acute peripheral lesion often causes spontaneous nystagmus with horizontal and rotational components. The fast phase is directed away from the side of the lesion. Spontaneous nystagmus resulting of central origin can be purely vertical, horizontal or rotational. Positional nystagmus refers to nystagmus that is present only when the head is placed in an unusual position, for example, upside down. There are less specific neurological signs that may be associated with vestibular dysfunction that include conscious proprioception deficits (indicative of brainstem disease); Horner's syndrome (usually indicative of peripheral disease); cranial nerve deficits (multiple cranial nerve dysfunction usually indicates central disease, but facial nerve paresis can occur with central or peripheral disease); head tremor (indicating cerebellar disease) and an altered level of consciousness (indicative of central disease). The differentials for peripheral and central vestibular disease are discussed below. The next steps may be determined by the lesion localisation.
- A minimum database should be performed on all cats which should include hematology, serum chemistry, urinalysis and thoracic radiographs. If toxicity is suspected due to antibiotic administration (metronidazole and aminoglycosides), I would recommend immediate withdrawal of the medication. In most cases, there is resolution of the vestibular abnormality. In the absence of a systemic health concern, a practical approach can be taken with peripheral vestibular disease cats.
- Ancillary tests for patients with peripheral disease include otoscopic examination; imaging of the tympanic bullae with radiography, computed tomography (CT), or magnetic resonance (MR) imaging; and thyroid function testing. A brainstem auditory evoked response (BAER) test may be of value in examining the auditory portion of cranial nerve VIII (vestibulo-cochlear nerve) as well as potentially assisting in localizing the disease to the peripheral or central components. Diagnosis of central disease is based upon CT or MR imaging of the brain and analysis of cerebrospinal fluid (CSF).

CAUSES OF PERIPHERAL VESTBULAR DISEASE

Idiopathic vestibular syndrome is a common cause of peripheral vestibular disease in the cat. The onset of the vestibular disease may be so acute that is accompanied by vomiting, but this is not specific for this etiology. Postural reactions are normal in this disease, and cats do not have facial paresis or Horner's syndrome. This can be only by diagnosed by ruling out the other causes; however, it is the only differential of peripheral disease that will start to improve in 72 hours with no specific treatment. If the patient is closely monitored over this time course, marked resolution of the nystagmus can be seen. This will be followed by improved gait over a 7-day period and improvement of the head tilt over a 2-month period. The head tilt may never completely resolve. If there is evidence of facial nerve involvement or Horner's syndrome further ancillary tests should be considered.

Otitis Media / Interna

Up to 50% of cases of peripheral vestibular disease are due to otitis media / interna. Infection of the middle ear can cause vestibular disease due to the production and spread of bacterial toxins into the inner ear. The infection can directly damage the inner ear with spread to the labyrinth. The bacteria commonly responsible for this disease are *Staphylococcus* spp., *Streptococcus* spp., *E. coli* and *Pseudomonas* spp.

Nasopharyngeal Polyps

Polyps are pedunculated masses, which arise from the lining of the tympanic cavity, eustachian tube, or nasopharynx. Nonseptic otitis media / interna may occur secondary to occlusion of the eustachian tube due to a nasopharyngeal polyp and polyps may occur as a result of chronic middle ear infection or from ascending infection from the nasopharynx. Diagnosis may require advanced imaging if physical examination and skull radiographs are not helpful.

Neoplasia

Neoplasia of the structures of the ear includes squamous cell carcinoma, ceruminous gland adenocarcinoma, and lymphoma.

Ototoxicity

There are many drugs listed as being ototoxic and can potentially cause both vestibular dysfunction and deafness. The deafness caused by such drugs is often permanent whereas the vestibular disease may resolve or at least the dog may compensate for the abnormality. The most common topical drug implicated in this scenario is chlorhexidine.

Trauma

Head trauma may cause the onset of vestibular disease, which may be peripheral or central depending upon the severity of the trauma. Middle ear hemorrhage subsequent to a trauma may cause peripheral vestibular disease seen with or without facial paresis and Horner's syndrome.

CAUSES OF CENTRAL VESTIBULAR DISEASE

Inflammatory Disease

The common infectious diseases responsible for inflammation of the brain and its structures are feline infectious peritonitis (FIP), toxoplasmosis, bacterial infection, and cryptococcosis. While all the above infections can cause vestibular disease, they often have a multifocal central nervous system distribution and may also cause profound systemic abnormalities. The prognosis for each patient not only depends on the infectious etiology but also on the severity of the presenting signs, neurological as well as systemic.

Neoplasia

The most common tumors to cause central vestibular disease in cats are meningiomas and lymphomas located at the cerebello-medullary-pontine angle. Tumors of the forebrain can also cause central vestibular disease due to caudal transtentorial herniation with secondary compression of the brain stem.

Toxicity

Metronidazole toxicity can occasionally cause central vestibular signs in cats. Seizures have also been seen with this intoxication. An acute onset of signs may occur from 3 to 14 days after starting the antibiotic and has been seen with standard 30 mg/kg/day doses.

Cerebrovascular Disease

Cerebrovascular disease (CVD) may cause a peracute onset of central vestibular signs. Ischemia may be embolic or thrombotic and is the most common form of CVD; its causes may be due to sepsis, neoplasia, endocrine disease, hypertension, or may commonly be idiopathic. In some areas of the country this can result from aberrant parasite (Cuterebra) migration through the nervous system. Nontraumatic hemorrhage, the other form of CVD, is bleeding into the parenchyma of the brain that may extend into the ventricles. Recovery from this disorder can be complete but can depend on the underlying disorder.

STATUS EPILEPTICUS — LIFE AFTER DIAZEPAM

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Status epilepticus is a danger to the patient and a treatment challenge for the clinician. Although no evidence exists to indicate that early initiation of appropriate treatment improves the outcome in dogs with seizures, such evidence does exist for human medicine and remains an important basic tenet of treatment. The main goals of the treatment of SE are to simultaneously (1) evaluate and treat any underlying causes, (2) maintain adequate vital functions with prevention of systemic complications, and (3) terminate the seizure activity safely and quickly while minimizing treatment-related morbidity.

A team approach to patients in SE will be beneficial to accomplishing emergency stabilization, therapeutic intervention, and diagnostic investigation simultaneously. Concurrently, a medical history should be obtained from the owners or retrieved from available medical records.

Factors determining the drug to be used in SE are its ease of administration, time of onset, duration of effect, and its minimal effects on the cardiorespiratory function and level of consciousness. Unfortunately no single drug is ideal. The rate of brain entry of a drug is directly proportional to non-protein-bound drug serum concentration, lipid solubility, and cerebral blood flow. Therefore, SE is treated by intravenous (IV) infusion (to obtain high serum concentration) of lipid-soluble anti-epileptic drugs (AEDs). When a drug is selected to be used, sufficient time must be allowed for the drug to act before more of the same medication is used. If a single agent does not control the seizures, a second drug may be needed. If the combined effects of two drugs do not achieve cessation of seizures, alternative aggressive treatment such as general anesthesia should be considered.

The goals of anticonvulsant therapy in SE are to achieve cessation of clinical and electrical seizure activity and prevent its recurrence. Intravenous drug treatment for SE should be started without delay. This is necessary based upon the relationship between duration of SE and the extent of neurologic morbidity. This approach is also based upon experimental animal models that suggest that SE becomes progressively less responsive to treatment with diazepam.

BENZODIAZEPINES

Benzodiazepines (diazepam, lorazepam, midazolam, and clonazepam) are potent, fast-acting AEDs and therefore (particularly diazepam), are the preferred initial therapy in SE. None of the benzodiazepines are effective for chronic control of SE. They are a widely used class of sedative/tranquilizer and anxiolytic agents that differ widely in their time course and their central effects. These differences may be related to their pharmacokinetics, especially their distribution into and out of the central nervous system, which has been related to the drugs' lipophilicity and plasma protein binding. The lipophilicity of these compounds determines their rapid brain penetration after intravenous administration. Although the penetration is rapid, distribution equilibrium among all regions takes longer.

Their primary pharmacologic actions are probably related to a benzodiazepine receptor–mediated enhancement of gamma-aminobutyric acid (GABA)-ergic transmission, both pre and post synaptically. Benzodiazepines do not seem to alter the synthesis, release or metabolism of GABA but rather, potentiate its action at the receptor. The resultant augmented flow of chloride ions into cells decreases the ability of the cell to initiate an action potential. It seems that benzodiazepines prevent the spread of seizure rather than suppress the focus.

Adverse effects of intravenous benzodiazepines include respiratory depression, hypotension, and impaired consciousness. However, it has been suggested that there is a low incidence of respiratory depression with benzodiazepines because of the low density of binding sites in the brainstem.

Diazepam

Diazepam remains the first drug of choice for the treatment of SE in dogs and cats. The major metabolites of diazepam, nordiazapam (desmethyldiazepam), and oxazepam have up to 33% of the activity of the parent drug. The half-life of diazepam is 3.2 hours in the dog but the half-lives of the metabolites are slightly longer, up to 5.2 hours in the case of oxazepam. With its relatively brief duration of action, diazepam is not a definitive therapy for SE. However, because IV diazepam produces transiently high serum and brain concentrations of the drug, it can be a useful drug therapy. Because SE may end spontaneously, IV diazepam should not be administered to a patient presenting in a post-ictal state unless there is another seizure.

A dose of 0.5 to 1.0 mg/kg intravenously, up to a maximum dose of 20 mg, has been recommended for use in dogs and cats. This dose can be repeated to effect or twice within 2 hours. If the diazepam does not control the seizures, the use of phenobarbitone should be considered. Probably the most common and most dangerous error made in the management of SE is to treat repeated seizures with repeated doses of IV diazepam without administering an adequate loading dose of a longer-acting anti-epileptic drug. In this situation, the patient will continue to have seizures, toxic concentrations of diazepam or diazepam metabolites will accumulate, and serious morbidity may result from diazepam over-dosage.

Intravenous administration of diazepam may not be possible in some patients. It can be administered intramuscularly (IM), although absorption is not predictable. Rectal administration of diazepam may be considered initially at a dose of 0.5 to 2.0 mg/kg body weight depending upon whether the animal was being treated with phenobarbitone before the onset of SE. It may be necessary to use the higher dose in dogs receiving long-term phenobarbitone therapy. In previously untreated dogs, a per rectum diazepam dose of 1 mg/kg results in a mean time to peak plasma concentration of approximately 14 minutes.

Midazolam

Midazolam is a recently developed water-soluble benzodiazepine which is biotransformed by hepatic microsomal oxidation followed by glucuronide conjugation. Midazolam has been shown to have a wide margin of safety and a broad therapeutic index. It will diffuse rapidly across the capillary wall into the central nervous system and can be mixed with saline or glucose solutions. The mean plasma elimination half-life in dogs was shown to be 53 to 77 minutes following IV administration. Midazolam has a significant antiepileptic effect in humans proven to be caused by $GABA_A$ receptor stimulation, and has been shown to be more effective and safer for the control of seizures than comparable doses of diazepam.

Unlike diazepam, with erratic and incomplete intramuscular absorption, midazolam is rapidly absorbed following IM injection, with a high bioavailability, an early onset of sedation, and early clinical effects. The peak plasma concentration in dogs after IM administration was seen within 15 minutes. The dose for cats and dogs is 0.066 to 0.3 mg/kg IM or IV.

Lorazepam

Lorazepam s not as lipid-soluble as diazepam, and in animals, brain and cerebrospinal fluid concentrations of lorazepam rise at a slower rate than those of diazepam after IV injection. Pilot studies on the use of 0.2 mg/kg IV and 0.5 to 1.0 mg/kg per rectal (PR) lorazepam in normal dogs suggested that lorazepam may not be acceptable for PR administration because of an extensive first-pass effect. However, lorazepam can reach therapeutic blood concentrations when administered IV. At present, no data exist on the use of lorazepam in clinical cases.

PHENYTOIN SODIUM (DIPHENYLHYDANTOIN)

Although this drug is used in SE in humans, its IV injection can cause severe hypotension in dogs, and its IM absorption is extremely variable. Intramuscular injection of phenytoin can also cause adverse local reactions caused by precipitation at the site, including soft tissue sloughing. The half-life of phenytoin in the dog is variable, being as short as 3.65 hours after an 11 mg/kg IV dose. In the cat, phenytoin can have an effective duration of up to 108 hours, and this may be related to a decreased ability to conjugate the compound to glucuronic acid.

FOSPHENYTOIN

Fosphenytoin sodium is a phospate ester prodrug of phenytoin developed as a refinement of parenteral phenytoin. After administration, phenytoin is cleaved from the prodrug by phosphatases in the blood stream and several other organs. However, fosphenytoin is freely soluble in aqueous solutions and rapidly absorbed by the IM route. Fosphenytoin has no known anti-epileptic action before conversion. At present, there are no veterinary studies using this drug clinically as an AED.

BARBITURATES

Phenobarbital

Phenobarbital (PB) is a safe, inexpensive drug that may be administered orally, intravenously, or intramuscularly. Phenobarbital increases the seizure threshold required for seizure discharge and acts to decrease the spread of the discharge to neighboring neurons. The actions of this drug are primarily due to the enhancement of the inhibitory effects of GABA post-synaptically. There is also some inhibition of glutamate activity and the flux of calcium across the neuronal membranes.

The distribution of PB to the central nervous system may take up to 30 minutes, because of weaker lipophilicity in comparison with diazepam. This will need to be considered if the animal is still exhibiting generalized seizure activity. The recommended loading dose is 12 to 24 mg/kg IV, if immediate therapeutic concentrations are desired but this can induce a profound stupor with concurrent suppression of the cardiovascular and respiratory. Alternatively, the dose can initially be 2 mg/kg IV, repeating the dose every 20 to 30 minutes to effect and to a maximum total 24-hour dose of 24 mg/kg. The parenteral form can also be given IM, which is recommended if diazepam has already been administered. This will avoid the potentiation of profound respiratory and cardiovascular depression.

The depressant effects of PB on respiratory drive, level of consciousness, and blood pressure may complicate management of the SE patient, especially when administered after benzodiazepine. For these reasons, tracheal intubation may be necessary during IV administration of PB.

TREATMENT OF REFRACTORY SE

Status epilepticus that does not respond to a benzodiazepine or phenobarbital is considered refractory and requires more aggressive treatment. Potential reasons for resistant seizure activity include inadequate anticonvulsant doses, an uncorrected metabolic abnormality or the presence of an intracranial disease, such as a tumor. These patients often represent a difficult therapeutic problem. Short-acting anesthetic drugs are the most commonly used agents for treating resistant SE, as they have a rapid onset of action, short half-lives, and cause reductions in cerebral metabolic rates. These drugs should be used only in an intensive care setting because of the need for continuous blood pressure monitoring and ideally, central venous pressure monitoring. General anesthesia prevents tonic-clonic movements and allows control of respirations.

Continuous Benzodiazepine Infusion

This has been shown to be an effective mode of therapy in refractory SE in human and veterinary patients. The dose should be calculated hourly (0.1 to 0.5 mg/kg of body weight, every hour) and is usually diluted in 0.9% saline or in 5% dextrose in water (D5W), with the volume used being equal to the maintenance fluid requirement over the hour. The dose can be delivered with an infusion pump. The dosage rate should be reduced by 50% every 6 hours for at least two reductions before discontinuing the drug. Midazolam is completely water-soluble and has been shown to be an effective and safe therapy when administered by constant rate infusion.

Continuous PB Infusion

If bolus doses of PB are effective in controlling the SE but only for a short period of time, constant rate infusions of PB can be initiated but they can cause profound cardiorespiratory depression (2–4 mg/kg/hour) and can take a substantial time to wean once the patient is stable.

Propofol

In human cases of refractory SE, the use of IV infusions of anesthetic doses of propofol, 2,6-diisopropylphenol, has become standard. This approach has recently been evaluated in veterinary patients. Propofol has barbiturate- and benzodiazepine-like effects on the $(GABA)_A$ receptor and can suppress CNS metabolic activity. Propofol can be administered by IV bolus (1–2 mg/kg) or by constant rate infusion (0.1–0.6 mg/kg/min titrated to effect or up to 6 mg/kg/hr). The advantages of this drug over the barbiturates are its rapid clearance, chiefly eliminated by hepatic conjugation to inactive metabolites, and less profound hypotensive effects. However, this drug should be used with caution, preferably in settings where definitive airway control and hemodynamic support is possible, as hypoxemia secondary to apnea is a primary side effect as is myocardial depression. Experimental animal models have documented propofol's anticonvulsant effects.

Barbiturates

Thiopentone and pentobarbitone have potential, though unproven, cerebral protective effects in the management of SE. In adequate doses these drugs will almost always control the physical manifestations of seizures, but severe hypotension limits their safety. Pentobarbitone sodium, used at standard safe doses, is a general anesthetic with negligible anticonvulsant properties. Thiopentone has been associated with a higher degree of cardiac toxicity than pentobarbitone. Pentobarbitone should be given to effect not as a specific dose (3-15 mg/kg body weight IV) as there is tremendous individual variation in response. Patients treated with "barbiturate coma" commonly require an extended period of mechanical ventilation in an intensive care setting. In general, the side effects of barbiturate coma include depression of myocardial metabolism, vasodilatation with a decrease in venous return, and decreased cardiac perfusion. These effects can be minimized by the use of saline infusion and small doses of dopamine. Patients can develop poikilothermia and decreased urinary output during myocardial depression and hypotension. Neurologic evaluation is difficult because spontaneous respiratory responses and spontaneous movements cease.

Inhalational Anesthesia

Inhalational anesthetics have been recommended as a last resort in cases of resistant SE. The equipment and personnel necessary to administer inhalational anesthesia may not be readily available and can be cumbersome. Isoflurane, an inhalational general anesthetic agent, may be efficacious in the treatment of resistant SE. Not all of the volatile anesthetic agents have anti-epileptic potential, however; enflurane may actually increase seizure activity. Isoflurane does not undergo hepatic metabolism, has a rapid onset of action and has been extensively studied. Obviously, isoflurane therapy necessitates ventilation and intensive care monitoring, and hypotension may occur during therapy.

NEUROLOGIC MANIFESTATIONS OF CANINE AND FELINE ENDOCRINOPATHIES

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Endocrine diseases can adversely affect the function of the neuromuscular, peripheral, and central nervous systems through a variety of pathophysiologic mechanisms, including direct invasion of neural elements, depletion of cellular energy substrates, creation of ionic/osmolar imbalances, vascular compromise, and from multiple and unknown mechanisms. In many instances, neurologic dysfunction constitutes only a fraction of the constellation of polysystemic clinical signs that define many veterinary endocrine diseases. However, in certain cases episodic and sometimes vague neurologic dysfunction can be the primary or only historical or clinical manifestation of the underlying endocrinopathy.

ENDOCRINOPATHIES WITH DIRECT NEUROINVASIVE POTENTIAL

In these instances, neurologic dysfunction results from the direct invasion of neural parenchyma or compression of neural elements from an expanding functional endocrine neoplasm.

Pituitary-Dependent Hyperadrenocorticism (PDH)

Dogs and cats with PDH can demonstrate a variety of specific (seizures, thalamocortical blindness, and ataxia) and non-specific (lethargy, mental dullness, anorexia) signs of CNS dysfunction. In small animals with pituitary macrotumors (ie, mass > 1 cm in height), clinical signs may result from the direct compression of the brain parenchyma by the tumor or secondary to edema or obstructive hydrocephalus. However, a significant proportion of dogs with clinical and biochemical evidence of PDH and clinical signs of intracranial dysfunction examined with magnetic resonance imaging (MRI) by the author have no evidence of pituitary macrotumors or other observed cause for the neurologic disease Fractionated radiotherapy of the brain should be considered in cases with confirmed PDH and pituitary masses visible on intracranial imaging studies, as the severity of the neurologic deficits are a significant and negative prognostic indicator dogs with PDH and pituitary macrotumors.

Feline Acromegaly

In cats, excessive secretion of growth hormone (GH) most often results from functional neoplasia of pars distalis somatotrophic cells. The vast majority of cats with acromegaly have concurrent insulin-resistant diabetes mellitus (DM), and the predominant clinical signs present are reflective of poorly controlled DM, with the exception that many cats with acromegaly gain weight over time. Affected cats may also have inferior prognathism. Neurologic signs displayed by cats with acromegaly can consist of CNS signs (obtundation, ataxia, thermoregulatory abnormalities, adipsia, seizures) due to an expanding pituitary mass, and/or generalized or pelvic limb weakness and a plantigrade stance due to diabetic neuropathy. Many cats with acromegaly have a pituitary mass visible on computed tomography (CT) or MRI, which often extends into the suprasellar area. Definitive diagnosis of acromegaly requires documentation of elevated circulating GH concentrations. Pituitary irradiation has been used successfully to treat feline acromegaly.

ENDOCRINOPATHIES ASSOCIATED WITH NEURONAL ENERGY SUBTRATE DEPLETION

The pathophysiologic hallmark of these diseases is failure of generation, delivery, or utilization of necessary energy substrates to the nervous system (glucose, oxygen, and thiamine).

Pancreatic B-Cell Neoplasia (Insulinoma) and Hypoglycemia

The brain is a continually and extremely metabolically active organ. Sustained normal brain function is completely dependent on continual delivery of oxygen and glucose. Glucose is delivered to neurons by facilitated transport that is non-insulin dependent, and maintenance of euglycemia within the brain is dependent on a concentration gradient to allow for normal facilitated transport. Thus, CNS signs resulting from neuroglycopenia include seizures, stupor or coma, thalamocortical blindness, and ataxia in animals with insulinoma. However, a subset of dogs with functional B-cell neoplasia present with a clinical picture reflective of a generalized peripheral neuropathy, and histologic studies of nerve biopsies from some of these patients have demonstrated mixed motor and sensory axonopathies. The pathogenesis of insulinoma-associated polyneuropathy is poorly understood and may be the result of metabolic disease from chronic hypoglycemia, insulin toxicosis, or immune-mediated disease (shared onconeural antigens). Canine insulinoma-associated CNS signs and peripheral neuropathy can resolve with antineoplastic therapy.

ENDOCRINOPATHIES RESULTING IN IONIC/OSMOLAR IMBALANCES

Disorders in this category are primarily the manifestation of disordered neurotransmission that arises due to imbalances of normal cellular and interstitial electrochemical and osmolar gradients (i.e. electrolyte disturbances). Clinically, endocrinopathies that result in electrolyte deficiencies or osmotic imbalances can be associated with clinical signs of abnormal neuromuscular transmission or encephalopathy.

Hypoparathyroidism and Hypocalcemia

Calcium homeostasis is crucial in the physiology of normal neuromuscular function, as it is essential for the release of acetylcholine at the neuromuscular junction and for the contraction of muscle. When the ECF concentration of calcium declines, the excitability of nervous tissue increases due to increased neuronal membrane permeability. Although these changes occur in the central and peripheral nervous systems, they usually manifest clinically in the peripheral nervous tissues. The increased excitability of nervous tissue in the presence of hypocalcemia results in tetany, which is the intermittent contraction of muscles. Clinical features of primary hypoparathyroidism in dogs and cats involve intermittent neuromuscular signs such as facial rubbing, muscle fasciculations, cramping, generalized tremors, or stiffness of the gait. Seizures may also be observed. Many owners report that the observed neurologic signs are exacerbated by excitement, exercise or stress, and thus may be reflective of latent tetany. The remainder of the physical examination in most animals with hypoparathyroidism is usually unremarkable, as is the neurologic examination between visible episodes of tetany. Neurologic signs may be vague in some cases. The diagnosis of primary hypoparathyroidism is one of exclusion, but is strongly supported by the presence of hypocalcemia (total and ionized), hyperphosphatemia, normal renal function, and an absolute or relative deficiency of PTH. Emergency therapy for hypocalcemic tetany involves parenteral calcium administration, and primary hypoparathyroidism is chronically treated with oral vitamin D and calcium supplementation. In rare instances, the author has observed animals with hypoparathyroidism that have had various clinical manifestations of tetany that have been refractory to parenteral calcium therapy. Severe hypomagnesemia was identified in these cases, and once corrected, the tetany resolved with appropriate calcium supplementation.

Hyperthyroidism, Primary Hyperaldosteronism, and Hypokalemia

Generalized muscular weakness and cervical ventroflexion are uncommon clinical complaints in cats with hyperthyroidism, but when present are usually severe. Hyperthyroid cats with significant muscular weakness may have the apathetic variant of hyperthyroidism and concurrent hypokalemia from renal failure.

Hypokalemia is the biochemical hallmark of aldosterone secreting adrenal neoplasms, which have been rarely reported in cats and dogs. Although rare, persistent or episodic hypokalemia associated muscular weakness is a predominant clinical feature of primary hyperaldosteronism in small animals. In addition, hyperaldosteronism, especially in cats, may be accompanied by systemic hypertension and clinical signs consistent with hypertensive encephalopathy (see below). Hyperaldosteronism is diagnosed by demonstration of an adrenal mass with diagnostic imaging and elevated serum aldosterone concentrations. The treatment of choice is adrenalectomy.

Hypoadrenocorticism and Hyponatremia

Water intoxication is the term used to describe the pathology that results from primarily acute hypoosmolality from hyponatremia, and is characterized by generalized cerebral edema. Alterations in consciousness, seizures, ataxia, vomiting, and weight gain are signs reported in hyponatremic animals. However, neurologic signs are not usually apparent until the serum sodium concentration is $\leq$ 120 mEq/L. Chronic hyponatremia, such as that which occurs in most cases of primary hypoadrenocorticism resulting form the insidious destruction of the adrenal cortex, rarely causes clinically significant neurologic signs that are directly attributable to hyponatremia. Chronic hyponatremia allows for adaptive solute translocation, which safeguards against the development of cerebral edema. Transmembrane pumps are synthesized within neurons and glial cells which extrude cations and amino acids into the extracellular fluid (ECF), which serves to equilibrate the extra- and intracellular fluids (ICF). Adaptive solute translocation is believed to occur over several days.

Another important syndrome that can result from any naturally occurring or iatrogenic osmotic shift is called osmotic myelinolysis. In the veterinary literature the syndrome has been occasionally and erroneously referred to as central pontine myelinolysis, mainly because morphologic lesions are often most apparent in the basis pontis in humans. However, in small animals myelinolysis often occurs in extrapontine locations, and the thalamus has been the site most often affected in veterinary patients with myelinolysis. Osmotic myelinolysis has been associated with overzealous treatment of chronic hyponatremia in dogs with hypoadrenocorticism. Osmotic myelinolysis is theorized to develop as a result of rapid ion fluxes across the blood–brain barrier that disrupts normal homeostatic adaptive mechanisms that exist to combat the underlying abnormality. In the case of chronic hyponatremia, rapid administration of sodium rich fluids introduces large amount of sodium into a brain that has already equilibrated its ECF and ICF through adaptive solute translocation, and ultimately results in cellular dehydration. Dehydrated axons shrink and separate from their myelin sheaths which subsequently causes demyelination to develop several days later. Histologically osmotic myelinolysis is associated with nearly total myelin loss in affected areas, oligodendroglial degeneration, and preservation of axons and neuronal cell bodies.

The clinical signs associated with osmotic myelinolysis in animals include depression, weakness, and ataxia that may progress to UMN tetraparesis, hypermetria and myoclonus. Neurologic signs typically develop 2 to 7 days after treatment is initiated, and are potentially reversible with time. The MRI features of osmotic myelinolysis include non-enhancing, bilaterally symmetric T2 and FLAIR hyperintensities within the thalamus or cerebrum, which is suggestive of an increase in water content. Myelinolysis can be avoided by the judicious correction of chronic hyponatremia, and the rate of increase in the serum sodium concentration should not exceed 0.5 mEq/L/hr, in order to minimize the neurologic complications associated with osmotic shift, and the serum sodium concentration should be serially monitored during therapy.

ENDOCRINOPATHIES ASSOCIATED WITH VASCULAR COMPROMISE

Cerebrovascular accident (CVAs), which are often referred to as strokes, are clinically characterized by persistent, acute onset, focal intracranial neurologic deficits, and can occur secondary to both hemorrhage (hemorrhagic stroke) and infarction (ischemic stroke). Hemorrhagic stroke results from rupture of a blood vessel wall, while ischemic stroke occurs due to temporary (vasospasm) or persistent occlusion of the vessel lumen (thrombus, embolus, intramural vascular disease). By definition, brain infarctions are composed of necrotic neuronal and glial elements, and represent the final morphologic manifestation of severe, acute to subacute, ischemic injury. Transient ischemic attacks (TIA) are focal, transient neurologic disturbances that result from short-duration ischemia, and may not be associated with morphologic lesions on CT or MR, although TIA may precede overt stroke. With supportive care, partial to complete recovery is possible in many animals experiencing CVAs; however, identification and treatment of any associated endocrine or other metabolic diseases is of paramount importance, as the presence of coexistent disease is a negative prognostic indicator and important risk factor for recurrent stroke in dogs.

Diabetes Mellitus, Hypothyroidism, Hyperadrenocorticism and CVA

Ischemic brain infarctions have been reported to occur in dogs and cats with these endocrine disorders, and can have any topographic distribution within the brain. Circling, seizures, thalamocortical blindness, cerebellar signs, and central vestibular dysfunction are frequently reported clinical signs associated with CVAs in dogs. Hypothyroidism and diabetes mellitus has been reported to be an underlying cause of and risk factor for the development of atherosclerotic vascular disease, and hypercholesterolemia and hyperlipidemia are common in dogs with atherosclerosis and hypothyroidism and diabetes mellitus. Brain infarctions have also been documented in small animals with cerebrovascular atherosclerosis, and illustrate one potential pathophysiologic mechanism responsible for the CVAs associated with small animal endocrinopathies. Atherosclerotic vascular disease may result in brain infarction through artery-to-artery thromboembolic or local vascular stenotic and thrombotic mechanisms. The hypercoaguable state that exists in patients with hyperadrenocorticism may also contribute to the development of CVA.

Diabetes Mellitus, Hyperthyroidism, Pheochromocytoma, Hyperadrenocorticism, Hyperaldosteronism, and Hypertensive Encephalopathy

Hypertensive encephalopathy is an acute neurologic syndrome that is precipitated by an abrupt rise in systemic arterial blood pressure. In canine and feline models of both spontaneous and experimental hypertension, it appears that hypertensive encephalopathy occurs most commonly in cases of severe and/or rapidly developing systemic hypertension. Clinically, hypertensive encephalopathy is characterized by ataxia, vomiting, nausea, seizures, and visual disturbances that often occur in association with concurrent evidence of other end-organ damage (retinal detachments, etc.). Hypertensive encephalopathy occurs when the systemic blood pressure exceeds the upper limits of cerebral vascular autoregulation (usually > 220 mmHg systolic) and forces overdistension of cerebral arterioles. This results in disruption of the endothelial tight-junctions that comprise the blood–brain barrier, and the formation of vasogenic edema. Hypertensive encephalopathy is associated with characteristic MR findings of primarily subcortical white matter edema without infarction in the posterior cerebral hemispheres, which may extend into the brainstem and cerebellum. Routine and serial monitoring of arterial blood pressure should be performed in small animals with diabetes mellitus, hyperthyroidism, pheochromocytoma, and hyperadrenocorticism, especially in the face of acute encephalopathic signs.

NEUROLOGIC COMPLICATIONS OF ENDOCRINOPATHIES WITH A COMPLEX OR UNKNOWN PATHOGENESIS

Hypothyroidism and Peripheral Mono- or Polyneuropathies

Several clinical manifestations of peripheral neuropathic dysfunction have been described in dogs with spontaneous hypothyroidism including generalized weakness associated with a diffuse lower motor neuron tetraparesis; isolated or multiple cranial neuropathies with an apparent predilection for involvement of the facial, vestibular division of the vestibulocochlear, and trigeminal nerves; and megaesophagus and laryngeal paralysis. There currently is little direct evidence that there is a direct-cause and effect relationship between these syndromes and hypothyroidism. The proposed pathogenesis of disease in these instances is unknown, but may include myxedematous compression of peripheral nerves as they exit neural foraminae, segmental demyelination of nerves, or metabolic axonopathy. Changes are reversible with levothyroxine therapy in some dogs. Repeated observations by the author involving both experimental and spontaneous cases of canine hypothyroidism suggest that coexistent thyroid deficiency impairs the normal regenerative ability of the peripheral nervous system in response to concurrent insult, rather than being the causative etiology for observed neurologic deficits.

Myxedema Coma and Hypothyroidism

Myexdema coma is a rare but life-threatening complication of hypothyroidism that is most often precipitated by a concurrent disease in humans, such as infection or cardiac failure. In addition to stupor or coma, and more classic dermatologic signs of hypothyroidism clinical signs observed in cases of myxedema coma include bradycardia, hypoventilation, hypothermia without shivering, and cutaneous (non-pitting) myxedema. The pathogenesis of myxedema coma is complex and likely involves cerebral hypoxia/ischemia, impaired cerebral energy metabolism, and possibly osmotic imbalances associated with hyponatremia. Prompt recognition and treatment with intravenous levothyroxine and aggressive supportive care may allow for recovery.

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DISORDERS OF ABNORMAL INVOLUNTARY MOVEMENT: A VIDEO CASE-BASED REVIEW

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Disorders of abnormal involuntary movement (DAIM) are characterized by the presence of involuntary muscle contractions in conscious patients, and can arise from disease of skeletal muscle, peripheral nerves, or the central nervous system. Thus, when discussing DAIM in the context of the conscious patient, we are purposefully neglecting sleep- and seizure-related movement disorders, of which there are many. In veterinary medicine, DAIM are poorly classified and defined, partially because of the inconsistent nomenclature that the profession uses to clinically describe the numerous types of involuntary muscle contractions that occur in dogs and cats. This review is intended to facilitate the small animal practitioner's understanding of the classification, pathophysiology, diagnosis, and treatment of veterinary DAIM via an illustrated case-based approach.

CLASSIFICATION OF DAIM

When presented with a patient with DAIM, the first requirement is to determine whether the observed clinical abnormalities are representative of excessive (hyperkinetic) or reduced (bradykinetic) muscle activity. The vast majority of veterinary DAIM described to date fall into the category of hyperkinetic diseases. Ideally, the nomenclature of DAIM should consistent of terms that reflect both the primary phenotypic manifestation of the disease, but also the specific pathophysiologic abnormality that results in generation of the observed involuntary muscle contraction. The rapid development and application of genomic analysis within the biomedical sciences has allowed for the identification of the specific genetic defects that cause selected veterinary DAIM. However, DAIM have been traditionally classified in veterinary medicine based on the cardinal type of abnormal muscle contraction present, with myoclonus, myokymia/neuromyotonia, myotonia, tetany/tetanus, and tremor being commonly used terms. It can be difficult to determine the neuroanatomic origin of the abnormal muscle contraction based purely on its clinical appearance (and thus, in many instances, the specific pathophysiologic basis for the observed disorder is unknown). The classification of veterinary DAIM is likely going to be further complicated by a phenomenon known as phenotypic variability, in which the clinical manifestations of a disease can be heterogeneous among individuals despite a commonly shared genetic defect.

DAIM PHENOTYPES CAUSED BY DISEASE OF SKELETAL MUSCLE

Myotonia

Myotonia is a persistent, sustained muscle contraction with delayed relaxation, and arises from congenital or acquired disorders of myocyte membrane conductance. Myotonia congenita has been best described in the miniature schnauzer and Chow Chow breeds of dogs, but has been sporadically reported in several other breeds. Clinical signs typically are present within the first several months of life in affected dogs, and consist of a stiff, "saw-horse" like gait that may improve with exercise, hypertrophy of the glossal and proximal limb musculature, and percussion dimpling of muscles. Some dogs experience respiratory distress and/or dysphagia from hypertrophied tongue and pharyngeal muscles. The electrophysiologic hallmark of myotonia is a characteristic high-frequency, waxing and waning (myotonic) discharge which is detectable with electromyography (EMG). In the miniature schnauzer, myotonia congenita has been genetically characterized as an autosomal recessive disorder resulting from a myocyte voltage-gated chloride-channel mutation which causes myocyte hyperpolarization, and a genetic test is available for this breed. Myotonia congenita can be treated with anti-arrhythmic drugs, such as mexiletine (2 mg/kg PO q 8–12 hrs) or procainamide, and dogs with myotonia congenita can adapt well if they avoid cold temperatures and adhere to a regular exercise regime.

Acquired myotonia/pseudomyotonia most often occurs as a secondary complication of spontaneous or iatrogenic hyperadrenocorticism, but has also been reported in association with myotonic dystrophies or as a clinical sequlae of 2,4-D herbicide intoxication. Acquired myotonia is best treated by identification and, when possible, treatment of the underlying cause.

DAIM PHENOTYPES CAUSED BY DISEASE OF NERVOUS SYSTEM

Abnormal, involuntary skeletal muscle contractions that result from lesions of the central or peripheral nervous system can be classified as myokymia/neuromyotonia, tetany/tetanus, myoclonus, tremors, or other movement disorders. Some sources use the term *myoclonus* as an inclusive term to refer to all abnormal involuntary muscle movements (tremors) that arise from disease of the nervous system.

Myokymia and Neuromyotonia

Myokymia and neuromyotonia are electrophysiologically distinct but clinically related conditions in which persistent muscular contraction results from hyperexcitability of motor axons or motor nerve terminals. Myokymia appears clinically as a persistent, undulating or wavelike muscle contraction that spreads across the muscle surface that persists during wakefulness and sleep, and can occur as a generalized disorder or focally affecting the face or limb muscles. Myokymic discharges appear as regular or irregular bursts of single motor unit potentials that can occur as doublets, triplets, or multiplets with a discharge rate of 5–150 Hz on EMG. Neuromyotonia results in persistent muscle stiffness that can range in severity from being subclinical to causing severe contractures of the distal extremities (claw-like deformity) and face (facial grimacing). Neuromyotonic discharges appear similar to myokymic discharges on EMG, but occur at higher frequencies (15–300 Hz), begin and end abruptly, and have an amplitude that typically wanes over time.

Myokymia and neuromyotonia can result from disease at any level of the motor axonal pathway. In humans, myokymia and neuromyotonia have been reported to occur secondary to brain neoplasms, a variety of immune mediated diseases, rattlesnake envenomation, radiation-induced neural injury, and lymphoid malignancies. Myokymia of undetermined origin has been reported in both dogs (especially terrier breeds) and cats, and can be treated with drugs such as gabapentin, phenytoin, mexiletine, and carbamazepine. Some dogs with myokymia will also demonstrate episodic collapse associated with hyperthermia.

Tetany/Tetanus

Tetany is the intermittent contraction of extensor muscle groups, while *tetanus* is the term used to refer to the continuous contraction of the extensor muscles. In dogs, the most common cause of tetany is periparturient hypocalcemia or hypoparathyroidism, and thus animals with tetanic contractions should have a serum biochemical profile and ionized calcium performed. Calcium and vitamin D supplementation are the treatments of choice.

Tetanus primarily results from intoxication with the exotoxins produced by the anaerobic bacterium *Clostridium tetani.* After colonization of a necrotic wound, the exotoxin tetanospasmin is produced by resident clostridial spores, ascends to the CNS via peripheral nerves, and ultimately blocks the release of the inhibitory neurotransmitter glycine from interneurons in the brain and spinal cord which results in the continual excitation of motor neurons and continuous muscle contractions. Clinically, both generalized and localized forms of tetanus can affect dogs and cats, with the local form often being limited to a single limb or the facial muscles. When the facial muscles are affected, a grimacing expression called risus sardonicus and trismus can develop. Tetanus is most often diagnosed based on historical and clinical findings. Treatment of tetanus consists of wound debridement, parenteral metronidazole or penicillin treatment, administration of tetanus antitoxin, and muscle relaxants (diazepam, methocarbamol, or barbituates), provision of nutritional support, and minimizing environmental stimulation. With supportive care, recovery from tetanus typically occurs within several weeks, but can take several months in severe cases.

Tremors

Tremors can be sporadic or repetitive in nature. Repetitive types of tremor (Table 1) are much more common in veterinary medicine, with sporadic tremorigenic conditions likely being an underlying manifestation of a seizure disorder. Repetitive tremors are further characterized based on their appearance at rest (typically postural tremor that affects antigravity muscles), during voluntary contraction of skeletal muscle (action-related tremor), or persistence during all conditions.

Constant repetitive tremor (myoclonus) is most often associated with canine distemper encephalomyelitis, and can be observed in association with other neurologic complications of distemper viral infection. The myoclonic contractions rarely affect the entire body, usually affecting a single limb or the jaw. Muscle contractions are rhythmic and worse at rest, but persist in all conditions. The pathophysiologic mechanism for the development of myoclonus is hypothesized to be an aberrant lower motor neuronal pacemaker. Some dogs with myoclonus will respond to treatment with lidocaine or procainamide. Once myoclonus is present, the affected muscle groups typically remain static.

Intention tremor is often a feature of numerous congenital (ie, hypoplasia) and acquired degenerative, inflammatory, neoplastic, and vascular diseases of the cerebellum. Cerebellar tremor primarily results from disorders that diffusely affect the cerebellar cortex. Thus, animals with intention tremor often have obvious evidence of a coexistent symmetric cerebellar ataxia characterized by a wide-based stance, truncal sway and dysmetria. Treatment of cerebellar associated tremor is best directed at identification and treatment of the primary disease.

Congenital disorders of myelin formation (dys- or hypomyelination) cause diffuse, action-related repetitive tremors that are apparent at birth or at the time of ambulation. The tremors in dogs with congenital disorders of CNS myelination are typically diffuse, although often much more pronounced in the pelvic limbs, and can cause a dramatic bouncing or bunny-hopping pelvic limb gait. CNS hypomyelination may also be accompanied by other clinical signs of brain dysfunction such as seizures, and severely affected individuals may be incapable of ambulating or eating. The clinical signs associated with hypomyelination may improve and or resolve with maturation in puppies of some breeds (particularly Chow chows and weimeraners) with congenital hypomyelination.

Steroid-responsive tremor syndrome is the term the author uses to describe the acute-onset, non-progressive diffuse, action-related repetitive tremors that commonly affects small and toy breed dogs (White shaker dog syndrome, West Highland white terrier, Maltese), but can affect dogs of any breed or coat color. The disease is suspected to be an autoimmune disorder. Some affected dogs have had MRI and CSF evidence of a non-suppurative meningoencephalitis. Most dogs have a rapid and dramatic response to treatment with prednisone (initially 2–4 mg/kg/day PO), that can usually be tapered and eventually discontinued over a several week to month period. Occasionally, continuous alternate day or pulse steroid therapy may be required to maintain remission. Relapses have also been observed following discontinuation of treatment.

Table 1. Classification of Repetitive Tremors

Repetitive Tremor Type	Clinical Appearance	Possible Causes
Constant repetitive tremor (myoclonus)	Occur during action, but persist at rest, and even during sleep; often affects 1-2 limbs or the jaw, rarely the whole body	• Canine distemper encephalomyelitis* • Other nonsuppurative encephalitides
Action-related tremor of the head/neck (intention tremor)	Rapid, fine tremor present during goal-directed movement (eating/drinking); often associated with cerebellar ataxia	Cerebellar disease*
Diffuse, action-related, repetitive tremor	Whole body, rapid tremor that occurs during action; dissipates during rest/sleep	Congenital or acquired disorders of myelin • Dysmyelination • Hypomyelination* • Demyelination Intoxications • Mycotoxins, lead, macademia nuts, organophosphates, metaldehyde, stimulant drugs Idiopathic (Immune-mediated) • Steroid-responsive tremor (White shaker) syndrome*
Episodic postural repetitive tremor of the head and neck	Episodic, non-progressive tremors limited to the head	Idiopathic "Head bobbers"* • Doberman, Bulldog, Boxers, Boston terriers
Diffuse postural repetitive tremor	Rapid tremor possibly occurring in all antigravity muscles at rest; tremor abolished during movement	Breed-related orthostatic tremor* • Great Dane, Mastiff, others
Postural repetitive tremor of pelvic limbs	Rapid tremors usually confined to pelvic limbs of standing geriatric dogs	Benign, essential tremor

*Diseases discussed

Episodic postural repetitive tremor of the head and neck is prevalent in the Doberman, English Bulldog, and Boxer breeds of dogs. Clinically, tremors seem to be unpredictably sporadic, may cause vertical or horizontal movement of the head, do not appear to be progressive, and have not been reported to be associated with the development of other neurologic deficits. Laymen often refer to these dogs as "head bobbers or head shakers." The tremors disappear when the animal lies the head down or eats. Antemortem diagnostics tests (MRI exams, CSF) have been normal when performed. Therapy with anticonvulsants, such as phenobarbital and bromide, has been attempted in affected dogs with variable (and anecdotal) success.

A diffuse postural repetitive tremor (primary orthostatic tremor [OT]) has recently been recognized in Great Danes, Mastiffs, and other breeds of dogs. The tremors typically begin in the lower aspects of the legs, but can also involve the muscles of the head and face. In Great Danes, the tremors usually appear at 1 to 2 years of age, and affected dogs often appear reluctant to lie down and demonstrate what appears to be a constant "shivering" while standing suggestive almost of an involuntary dance. The tremors that are characteristic of the disease completely disappear when the dog walks, runs, leans against an object, or lies down. Auscultation of tremoring muscle reveals a sound that resembles a helicopter rotor. Great Danes with OT are typically otherwise healthy on physical examination, and generally do not have any significant abnormalities that are detectable on routine blood tests, radiographic examinations, CSF analysis, muscle and nerve biopsies, and even have normal MRI examinations of their brains. Diagnosis of OT requires documentation of the characteristic tremor pattern during a conscious (EMG) examination. OT appears to be an insidiously progressive disease, but some dogs can experience prolonged periods of clinical remission with gabapentin (10 mg/kg PO q 8–12 hrs) or phenobarbital (2 mg/kg PO q 12 hrs) therapy.

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CLINICIAN'S PERSPECTIVE: NONTRADITIONAL ANTICONVULSANT DRUGS FOR THE TREATMENT OF IDIOPATHIC EPILEPSY

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Small animals with recurrent seizure disorders represent a significant proportion of veterinary patients with neurologic disease evaluated at general, emergency, and specialty practices, and can present a significant management challenge to the attending veterinarian. Compared with what is known regarding the safety and efficacy of staple anticonvulsant drugs such as phenobarbital and bromide, the current body of knowledge regarding nontraditional anticonvulsant use in veterinary medicine is sparse, as there exist only a few reports of their clinical usage, primarily in small numbers of dogs with idiopathic epilepsy.

GOALS OF ANTICONVULSANT THERAPY IN VETERINARY MEDICINE

It should be stressed that there is no uniform definition of therapeutic "success," especially when considering that both idiopathic epilepsy and pet owners are extremely heterogeneous entities. Although the ideal goal of anticonvulsant therapy is to eliminate the seizures, this occurs infrequently, and is a largely unrealistic expectation, especially in those dogs that are considered refractory epileptics. The practical definition of success should therefore be to simultaneously reduce the frequency and duration/severity of the patient's seizures while simultaneously minimizing drug associated adverse effects.

INDICATIONS AND RATIONALE FOR PRESCRIBING NON-TRADITIONAL ANTICONVULSANT DRUGS

1) Adjunctive treatment for refractory epilepsy. Alternative anticonvulsants are often prescribed in cases that are classified as having refractory epilepsy, which has been reported to occur in 20% to 30% of canine epileptics. Generally, refractory epilepsy is considered to exist in an individual patient in the following circumstances:

- Dogs in which the desired therapeutic effect of combination AED therapy is never achieved despite appropriate treatment (pharmacoresistant epilepsy). A typical epileptic in this group continues to experience seizures of unacceptable frequency, severity, or length despite receiving adequate dosages of phenobarbital and bromide, as confirmed by therapeutic monitoring of blood concentrations of both drugs. The addition of a non-traditional anticonvulsant drug to an epileptic with pharmocoresistant seizures offers the possible advantage of suppression of the seizure focus through one or more alternative mechanisms of action on epileptogenic neurons (and in some cases glia) that may be additive and/or synergistic with the actions of barbituates and bromide. In some instances, doses of phenobarbital and/or bromide may eventually be lowered if a durable therapeutic response to the nontraditional anticonvulsant drug is observed.
- Dogs in which combination (phenobarbital and bromide) anticonvulsant therapy partially or sufficiently improves the seizure control, at significant expense to the quality of life of the pet and/or pet owner. This group of dogs cannot clinically tolerate combination therapy without unacceptable drug-related adverse effects (this is also an iteration of #2 below). In this subset of patients the addition of a nontraditional drug to the treatment regimen often allows for a dose reduction or discontinuation of phenobarbital or bromide and thus improvement or resolution of drug-associated adverse effects.

2) Pharmocokinetic profile of specific drug is optimal for individual patient. Examples in this category include:

- Epileptic dogs who require discontinuation of staple anticonvulsants due to the development of life-threatening adverse effects of phenobarbital (ie, phenobarbital-associated hepatotoxicity or myelosuppression);
- Animals with alterations in consciousness or mobility and secondary, symptomatic epilepsy attributable to known structural brain disease in which an anticonvulsant with minimal potential to cause or exacerbate sedation or ataxia is desired;
- Animals who have experienced previous idiosyncratic drug reactions and/or owners who wish to avoid long-term therapy with phenobarbital or bromide.

NONTRADITIONAL ANTICONVULSANT DRUGS-GENERAL INFORMATION

The drugs that will be reviewed here include zonisamide (ZNS), felbamate (FEL), gabapentin (GAB), and levetiracetam (LEV) all of which are commercially available because of their demonstrated efficacy in the treatment of human seizures disorders. Currently, usage of these drugs is based on clinician preference and on a trial and error basis, as objective and measurable clinical variables that allow for prediction of their potential therapeutic benefit in individual epileptics have not been identified. All of the mentioned drugs are more expensive than phenobarbital, primidone, and bromide. However, generic formulations of some of these agents are available and my personal experiences suggest that there can be substantial variability in individual drug prices between different drug distributors, large commercial pharmacies, and custom-compounding pharmacies.

Although limited clinical information is available at this time for all of these nontraditional agents, several clinical studies in dogs have demonstrated the potential for the development of the "honeymoon effect." This phenomenon is characterized by an initial positive therapeutic response (either real or perceived) to the prescribed anticonvulsant drug followed by a return of seizure control to a level similar to that which existed prior to the addition of the new drug after a variable period of time. Studies performed in dogs receiving zonisamide, levetiracetam, and gabapentin have reported a honeymoon effect that occurs in some dogs that have good initial responses to these drugs.

ALTERNATIVE ANTICONVULSANTS – INDIVIDUAL DRUG REVIEW (TABLE 1)

Zonisamide (ZNS)

ZNS is a sulfonamide drug that likely possesses several inherent anticonvulsive properties, including CNS GABAergic agonism, inhibition of neuronal voltage-gated Na^+ channels and T-type Ca^{++} channels, scavenging free radicals, and modulation of CNS dopaminergic metabolism. The major advantages of ZNS are its favorable pharmacokinetic profile in the dog, and its clinical efficacy. ZNS has a long $T_{1/2}$ (14–16 hours), which allows for twice daily administration in the dog. Of the drugs discussed, ZNS also tends to be the most expensive.

As ZNS is metabolized primarily by hepatic microsomal enzymes, its has been demonstrated that dogs receiving concurrent drug therapy known to induce hepatic microsomal enzymes (ie, phenobarbital) require nearly twice the dose of ZNS to achieve and maintain serum concentrations of ZNS compared with dogs receiving ZNS alone. For that reason, dogs receiving phenobarbital should initially be administered 10 mg/kg of ZNS PO q 12 hrs. In dogs not on drugs that induce hepatic microsomal enzymes, ZNS can be dosed at 5 mg/kg PO q 12 hrs. This dosing schedule will maintain ZNS concentrations within the recommended therapeutic range (10–50 µg/mL; although may be as high as 70 µg/mL in people). Therapeutic monitoring of ZNS is recommended, and trough concentrations should be measured approximately 7 to 10 days after initiating treatment or altering the dosage. Clinical pharmacology laboratories in some human hospitals may be able to accommodate therapeutic monitoring requests for ZNS.

Experimental and clinical studies evaluating the safety efficacy of subacute and chronic ZNS administration have been performed in dogs. Chronic ZNS administration was well tolerated clinically in normal beagles receiving up to 75 mg/kg/day. In one clinical study of 12 refractory canine epileptics, ZNS administration caused mild, clinically tolerable, often transient side effects (sedation, vomiting, and ataxia) in 50% of the dogs. The same study reported that ZNS treatment resulted in a 50% or greater reduction in the frequency of seizures in 7 of 12 dogs, and also allowed for a significant, concurrent reduction in the dosage of phenobarbital required to maintain seizure control in the majority dogs that responded.

ZNS is not only an effective add-on drug, but also can be used as monotherapy in those epileptics in which more traditional anticonvulsant drug, such as phenobarbital and bromide, are not reasonable therapeutic choices. The most common indication in which ZNS is administered as a single drug is in small-breed epileptics whose owners are averse to the common side effects associated with phenobarbital and bromide usage. It is also important to note that as more dogs are treated with ZNS, additional potential adverse drug effects have been possibly identified, some which may be related to the sulfonamide base of ZNS. Objective evidence exists that ZNS administration may adversely affect canine thyroid function, and ZNS has also been anecdotally reported to cause keratoconjunctivitis sicca.

Felbamate (FEL)

Felbamate is a dicarbamate anticonvulsant drug that is primarily (70%) renally excreted in dogs, with the remainder of the drug undergoing hepatic metabolism. Felbamate likely exerts its anticonvulsant effects through multiple mechanisms including potentiation of GABA-mediated neuronal inhibition, inhibition of voltage sensitive neuronal calcium and sodium channels, and blocking NMDA-mediated neuronal excitation. In addition, FEL may provide some neuroprotection against ischemia/hypoxia-mediated cell damage.

Studies in veterinary medicine have demonstrated that felbamate is efficacious for treating focal and generalized seizures in dogs, both when used as an add-on anticonvulsant drug or as a sole agent. The recommended initial dosage of felbamate is 15 mg/kg PO q 8 hrs. The dosage of felbamate can be increased every 14 to 21 days in 15 mg/kg increments if therapeutic benefit has not been noted with the initial dosage. The dosage may be further escalated in a similar fashion until satisfactory seizure control is obtained, adverse effects are noted, or the treatment becomes cost prohibitive. Felbamate is a safe drug, with clinically apparent toxicities usually not apparent until dosages approach 300 mg/kg/day. Therapeutic monitoring is not routinely performed with FEL. Until recently, FEL had been the author's tertiary anticonvulsant drug of choice. In my experience, approximately one half of refractory epileptics will experience an acceptable reduction in seizure frequency and duration when FEL is added to the therapeutic regimen, with the majority of those dogs requiring less than 180 mg/kg/day.

Another therapeutic advantage of felbamate is that its use is not associated with sedation. Therefore, FEL also offers the advantage of being useful for the symptomatic treatment of seizures in those patients with an alteration in consciousness due to structural brain diseases, such as meningoencephalitis, hydrocephalus, brain infarction, or brain tumor. Adverse effects are reportedly rare with FEL. Since felbamate undergoes hepatic metabolism, its use can result in life-threatening hepatotoxicity, especially when used as an add-on therapy in dogs concurrently on phenobarbital. FEL has also has the potential to cause reversible myelosuppression, generalized tremors in small breed dogs, and possibly keratoconjunctivitis sicca.

Gabapentin (GAB)

GAB is a synthetic analogue of the inhibitory neurotransmitter GABA. GABs anticonvulsant activity is mediated through multiple mechanisms including inhibition of neuronal sodium channels and potentiation of the release and action of GABA. GAB is well absorbed in dogs after oral administration, and undergoes both hepatic and renal metabolism. In the dog, it has been recommended that GAB be administered at 25-60 mg/kg body weight, divided q 8 hrs. GAB is usually prescribed at an initial dose between 10–15 mg/kg PO q 8 hrs, although one study reported a positive response in some refractory epileptics that were administered GAB twice daily. The dose may require escalation to 30–60 mg/kg PO q 6–8 hrs to produce a significant therapeutic effect in canine epileptics. Therapeutic monitoring it not usually necessary with GAB. My personal experiences with GAB when used as an add-on anticonvulsant in refractory epileptics suggest that it is safe, but is only marginally efficacious at improving seizure control, and can cause mild to marked sedation and pelvic limb ataxia in some cases.

Levetiracetam (LEV)

The mechanisms of action of LEV are currently poorly understood. In dogs, LEV has excellent oral bioavailability, does not apparently undergo hepatic metabolism, is primarily excreted unchanged in the urine, and has a $T_{1/2}$ of approximately 4 hours. Studies available from the manufacturer in dogs suggest that chronic administration of LEV is extremely safe and rarely results in adverse effects (primarily ataxia) within the routine therapeutic dose range. The major purported advantages of LEV are its large margin of safety and minimal potential for adverse drug effects.

LEV is initially administered at 20 mg/kg PO q 8 hrs. The dosage can be increased every 2 weeks in 20 mg/kg increments if therapeutic benefit has not been noted at the initial dosage. The dosage may be further escalated in a similar fashion until satisfactory seizure control is obtained, the treatment becomes cost prohibitive, or adverse drug effects are noted. Although possible, therapeutic monitoring is generally not necessary when using LEV, as the drug is safe, and there does not appear to be a correlation between serum drug concentration and therapeutic efficacy.

One clinical study reported a 50% reduction in seizure frequency in 15 epileptic dogs that received LEV as an add-on therapy. An additional study evaluated the use of LEV (20 mg/kg PO q 8 hrs) as an add-on to phenobarbital in four cats with recurrent seizures, three of which were presumed to have idiopathic epilepsy. Seizure control improved in 3 of 4 cats, and the drug was also well tolerated clinically, suggesting that LEV may be safe and efficacious in cats. My personal experiences in dogs suggest that LEV is effective at improving seizure control in select cases, but many initial responders will experience a "honeymoon effect" as previously described. In addition, LEV can occasionally result in transient sedation, and may cause or exacerbate anticonvulsant associated pelvic limb ataxia/parapresis in some dogs.

Table 1. Non-traditional Anticonvulsant Summary

Drug Name	Therapeutic Advantages	Initial Dose/ Formulations	Therapeutic Range	Potential Adverse Effects	Cost Comparison* (10 kg dog/month)
Felbamate (Felbatol– MedPointe)	Non-sedating Safe Objective efficacy Economical No Rx monitoring	15 mg/kg PO q 8 hrs 400 mg, 600 mg tablets, 600 mg/5 mL liquid	20–100 µg/mL	Hepatotoxicity– rare Myelosuppression– rare Tremors– rare KCS?	$85–115 using 400 mg capsule formulation
Levetiracetam (Keppra– UCB Pharma)	Safe– dogs and cats Objective efficacy No Rx monitoring	20 mg/kg PO q 8 hrs 250 mg, 500 mg, 750 mg, 1 g tablets and 100 mg/mL liquid	5–45 µg/mL	Sedation? Ataxia?	$90–120 using 250 mg tablet
Gabapentin (Neurontin– Parke Davis	Safe Economical No Rx monitoring?	10—15 mg/kg PO q 6-8 hrs 100 mg, 300 mg, 400 mg, 600 mg, 800 mg capsules and tablets	4–16 mg/L	Sedation– uncommon Ataxia	$45–60 using 400 mg capsule formulation
Zonisamide (Zonegran– Elan)	Safe Objective efficacy BID dosing	5–10 mg/kg PO q 12 hrs 50 mg, 100 mg capsules	10–50 µg/mL	Transient sedation– common Ataxia– common Vomiting– common Thyroid interference? KCS?	$95–120 using 100 mg formulation

*Prices represent listings for licensed US pharmacies in 2007

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ANALGESIC ALTERNATIVES FOR THE PAINFUL NEUROLOGIC PATIENT: PART 1 – PERINEURAL AND EPIDURAL TECHNIQUES

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Pain is the unpleasant sensory and emotional experience associated with actual or potential tissue damage. Clinical pain is caused by two sources—inflammation secondary to tissue damage or peripheral or central neural injury (neuropathic pain). The perception of pain is a complex and dynamic process that involves five major processes: transduction, transmission, modulation, projection, and perception (Figure 1), each of which represents a potential therapeutic target when treating pain.

PERINEURAL AND EPIDURAL ANALGESIA IN THE NEUROLOGIC PATIENT: AGENTS AND MECHANISMS OFACTION

When performing perineural and epidural techniques, cocktails of multiple classes of drugs are usually chosen to optimize therapy by targeting multiple components of the pain pathway, overlapping and extending the duration of the desired therapeutic effect, and minimizing adverse dose-related drug effects. Various combinations and formulations of local anesthetics, opioids, and corticosteroids are most commonly used by the author for both epidural and perineural techniques, but nonsteroidal anti-inflammatory drugs (NSAIDs) and N-methyl-d-aspartate (NMDA) antagonists have also occasionally been utilized for provision of epidural analgesia.

Local anesthetics, such as lidocaine and bupivicaine, provide analgesia by deactivation of neural sodium channels, whose activation is crucial for generation of nerve action potentials. Local anesthetics therefore block transmission of excitatory impulses in peripheral nerves as well as diminishing conduction and projection of nociception in the CNS. Opioids provide analgesic effects via inhibition of peripheral and central sensitization at numerous levels that are drug (opioid receptor) dependent. NSAIDs primarily interact with cyclo-xygenase enzymes to inhibit the production of prostanoids that are involved in the facilitation of pain transmission through peripheral/central sensitization as well as modulation. Ketorolac has been the primary NSAID the author has used in epidural applications. Corticosteroids also function by inhibiting the production of inflammatory mediators involved in the facilitation of pain transmission, but may additionally provide some neuronal membrane stabilizing effects that inhibit pain transmission, and can produce euphoria.

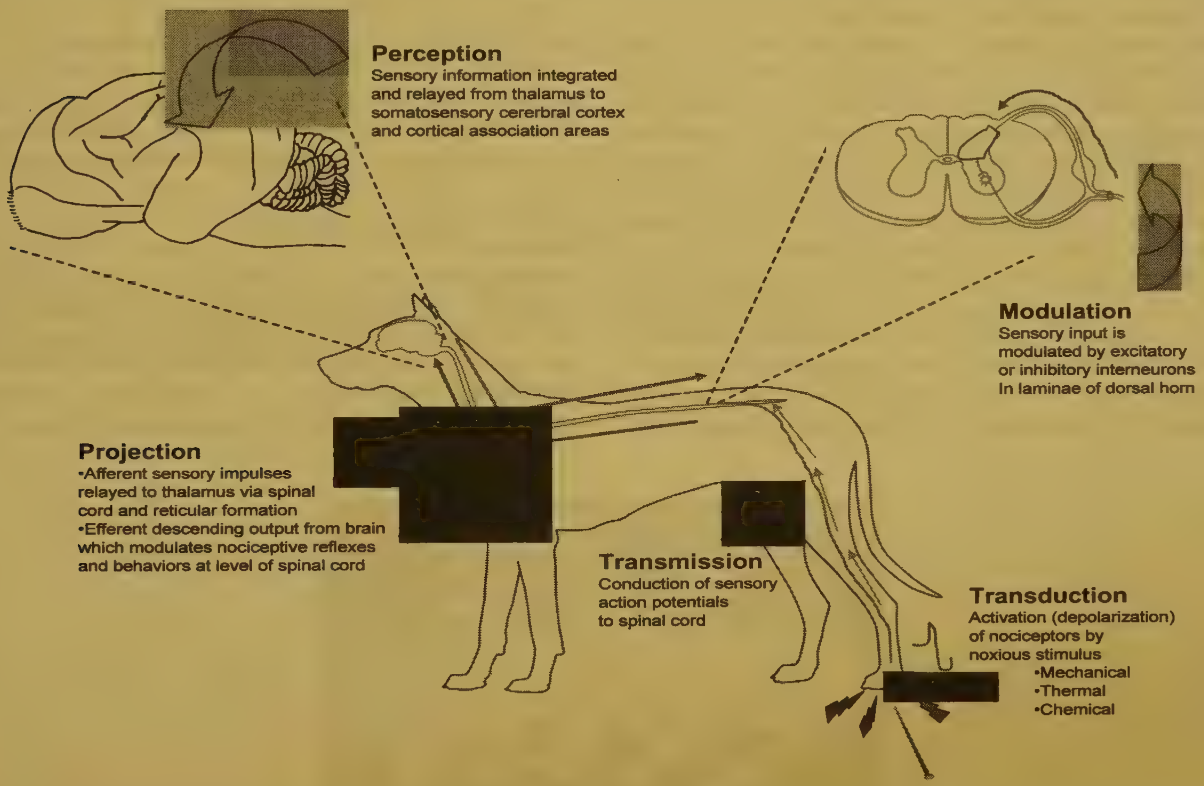
Perception
Sensory information integrated and relayed from thalamus to somatosensory cererbral cortex and cortical association areas
Modulation
Sensory input is modulated by excitatory or inhibitory interneurons In laminae of dorsal horn
Projection
•Afferent sensory impulses relayed to thalamus via spinal cord and reticular formation
•Efferent descending output from brain which modulates nociceptive reflexes and behaviors at level of spinal cord
Transmission
Conduction of sensory action potentials to spinal cord
Transduction
Activation (depolarization) of nociceptors by noxious stimulus
•Mechanical
•Thermal
•Chemical

Figure 1. The perception of pain is a complex and dynamic process that involves five major processes: transduction, transmission, modulation, projection, and perception, each of which represents a potential therapeutic target when treating pain.

PERINEURAL AND EPIDURAL ANALGESIA IN THE NEUROLOGIC PATIENT: INDICATIONS AND TECHNIQUES

The general indications for perineural and epidural anesthesia are:

- Provision of pre-emptive and/or adjunctive analgesia in patients undergoing (neuro)surgical procedures;
- Adjunctive palliative acute to subacute treatment of painful neurologic diseases (radicuolpathy/ radiculitis, meningomyelitis, mononeuropathy/ neuritis) in which the clinical efficacy of multimodal analgesia administered by other routes (orally, parenterally, or transdermally) is suboptimal, or adverse effects of analgesics administered by these other routes have been problematic or wish to be avoided;
- Diagnostic application of selective perineural blockade.

These techniques are often also administered concurrently with neuropathic pain modifying agents (see the following article, Analgesic Alternatives for the Painful Neurologic Patient: Part 2 – Neuropathic Pain Modifying Agents, in this proceedings).

Perineural Analgesia

Perineural techniques are primarily used by the author for the treatment of radiculopathy associated with degenerative neurologic conditions such as intervertebral disk disease, lumbosacral stenosis, or cervical spondymyelopathy, especially in cases in which surgical intervention is not an immediate option. In these instances, combinations of bupivicaine and long-acting corticosteroids are usually chosen (Table 1). The author most often uses results of diagnostic imaging procedures (radiographs, myelography, computed tomography, or MRI) to selectively deliver extraforaminal perineural analgesia. Extraforaminal delivery can usually be accomplished under sedation (benzodiazepine and opioid). A 20- to 22-gauge spinal needle is directed through the epaxial musculature to the affected vertebra to the approximate level of the intervertebral foramen. Targeting of the correct anatomic site is facilitated by radiographic, fluoroscopic, or ultrasound guidance. The level of the intervertebral foramen can be approximated by placement of the bevel of the needle on the cranial edge of the transverse process of the caudally affected vertebra where it joins the vertebral body (Figure 2). Prior to injection, aspiration should be performed to prevent intravascular injection. If significant resistance is encountered during injection, the needle should be redirected, as this may be suggestive of intraneural delivery. Extraforaminal injection may also provide local epidural effects if the infusate spreads transforaminally.

Extraforaminal perineural analgesia using combinations of local and long-acting agents can provide several (3 to 6) weeks of analgesia. When performed correctly, complications of this technique are rare. The most commonly encountered complication is failure to achieve adequate perineural blockade, which necessitates repeating the procedure. Selective extraforaminal perineural blockade has also been used by the author as a diagnostic tool to aid in the differentiation of the clinical significance of radicular involvement in cases with neurologic disease resulting from multiple complex regional abnormalities (ie, lumbosacral stenosis with evidence of bony canal stenosis, intervertebral disk protrusion, and foraminal stenosis). In these instances, a short-acting local anesthetic such as lidocaine is used as a single agent.

Epidural Analgesia

Neurosurgical procedures involving anatomic structures caudal to the diaphragm in which extensive concurrent manipulations of the vertebral column and/or neural elements are anticipated constitute a primary indication for provision of epidural analgesia in a pre-emptive surgical context. Examples would include foraminal disk extrusions, hindlimb amputation and/or hemipelvectomy for treatment of nerve sheath neoplasia, pelvic fractures with sciatic nerve root entrapment/trauma, treatment of spinal fractures/luxations, and partial corpectomy/ vertebrectomy with instrumented spinal fusion for treatment of vertebral neoplasia. In these cases, combinations of local anesthetics, opioids, and NSAIDs are used (Table 1), and epidural catheterization for continuous drug delivery is occasionally performed. Complications of epidural techniques include urine

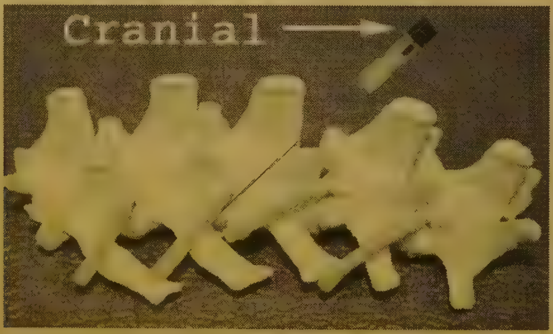

Figure 2. Extraforaminal delivery of perineural analgesia.

retention, transient deteriorations in motor function, and failure of the hair regrowth at the injection site.

Considering that compromised hindlimb motor function often is a major complaint in small animals with neurologic disease, and continual monitoring of motor function is important in patient management, drugs used for provision of epidural analgesia should ideally provide selective sensory blockade. This is most often accomplished with epidural cocktails consisting of various combinations of bupivicaine, morphine, and an NSAID, or corticosteroid.

Epidural techniques have also been used clinically by the author to provide palliative therapy for painful conditions for which surgery is not indicated or not an immediate option for the patient. Examples include canine immune-mediated cauda equina neuritis or lumbosacral stenosis. In these instances, low-dose bupivicaine and methylprednisolone are often delivered (Table 1). Epidural administration can usually be performed with sedation in dogs, but requires anesthesia in the cat. Epidural analgesia is most commonly delivered at the L7-S1 space, but occasionally can be administered at the sacrococcygeal space in large dogs.

In an ongoing study of medically treated dogs with umbosacral stenosis being performed by the author, the group that received epidural analgesia using bupivicaine and methylprednisolone had superior subjective pain scores and objective measurements of pelvic limb gait (as measured with serial force plating) at 1, 2 and 4 weeks than the group of dogs that were treated with NSAIDs alone.

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Table 1. Doses for Agents Used in Perineural and Epidural Anesthesia

Drug	Dose (concentration)	Indication	Comments
Bupivicaine	1–2 mg/kg (0.25%)	Perineural/Epidural[†]	Can also use 0.5% formulations
Bupivicaine	0.5–2 mg/kg (0.125%)	Epidural[†]	Dilute in 0.9% NaCl (0.2 mL/kg)
Lidocaine	4–6 mg/kg (0.5%)	Perineural	Can also combine with 1:200,000 epinephrine
Morphine	0.1–0.3 mg/kg	Epidural[†]	Dilute in 0.9% NaCl (0.2 mL/kg) Dose for preservative-free preparations
Ketorolac (dogs only)	0.2–0.4 mg/kg (diluted to 15 mg/mL)	Epidural[†]	GI ulceration risk with repeated use
Methylprednisolone acetate	1 mg/kg (40 mg/mL)	Epidural[†]/Perineural	Use 1 mL minimum epidural injection volume (dilute in 0.9% NaCl 0.2 mL/kg)
Betamethasone*	0.5 mL/10 kg body weight	Epidural[†]/Perineural	Use 1 mL minimum epidural injection volume
Triamcinolone acetonide[▼]	1 mg/kg (40 mg/mL)	Epidural[†]/Perineural	Use 1 mL minimum epidural injection volume

[†] Epidural injection volumes limited to $\leq$ 6 mL total volume when using multiple drugs

*Celestone Soluspan, Schering-Plough (3 mg/mL betamethasone acetate and 3 mg/mL betamethasone NaP)

[▼] Kenalog-40, Bristol-Myers Squibb.

ANALGESIC ALTERNATIVES FOR THE PAINFUL NEUROLOGIC PATIENT: PART 2 – NEUROPATHIC PAIN MODIFYING AGENTS

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Managing animal pain can be a significant challenge both to pet owners and practicing veterinarians, due to the difficulty in the assessment of pain and our poor understanding of the neurobiology of pain. Treating animals with neuropathic pain provides an additional level of frustration in that the classes of drugs most often used to manage chronic pain (nonsteroidal anti-inflammatory drugs [NSAIDs] and opioids) may not be sufficient to provide adequate analgesia to the neuropathic patient. This discussion will focus on the orally administered analgesic drugs available for the treatment of patients with chronic neuropathic pain.

WHAT IS NEUROPATHIC PAIN?

Neuropathic pain is described as the unpleasant sensory experience that results from dysfunction of the nervous system that follows direct injury to one or more components of the peripheral or central nervous systems. Clinically, neuropathic pain is characterized by the presence of hyperpathia (increasing pain after repetitive stimulation, which includes continued pain after removal of the stimulus and radiating pain to adjacent anatomic areas), allodynia (painful response to a normally innocuous stimulus), and hyperalgesia (a painful response that is interpreted as occurring disproportionate to the initiating stimulus). In veterinary medicine, neuropathic pain also tends to be used as a catch-all phrase that is probably more truly representative of multiple painful syndromes, each associated with different etiologies and pathophysiologic alterations. For example, in this discussion I will make no attempt to distinguish neurogenic pain, which results form injury to neural tissue, from neuropathic pain, because they may represent a continuum of disease and share similar clinical features.

The processes involved in transmission and perception of pain are complex and dynamic, and likely are somewhat variable among individuals of all species. In chronic states of pain significant peripheral and central sensitization, as well as changes in the perception of pain at the cerebrocortical level are usually present, and alterations in the nociceptive system are constantly evolving in response to stimulation (nociceptive neuroplasticity). Chronic exposure to pain can induce genomically mediated tissue alterations that can change the morphology and function of the neural pain pathways at virtually all levels. In some instances, these changes can be irreversible resulting in perceived pain even after removal of all inciting or persistent noxious stimuli (ie, phantom limb syndrome).

DRUG THERAPY FOR NEUROPATHIC PAIN

Several classes of drugs have shown promise in the treatment of chronic neuropathic pain, and therapeutic agents exist that target all components of the nociceptive system. Unfortunately, it is not currently possible to make disease and drug specific recommendations regarding neuropathic pain management for small animals, in part because neuropathic pain is an extremely heterogeneous condition. Therefore, the following principles should be adhered to when managing chronic neuropathic pain:

- When possible, identify and specifically treat the inciting disease;
- Multimodal drug therapy is preferred;
- Therapy should be optimized to the individual based on continual re-evaluations;
- Engaging, educating, and enabling the pet owner consistently provides the best assessment of the efficacy and toxicity of therapy.

Summaries of drugs and the author's approach to the treatment of neuropathic pain are provided in Figure 1 and Table 1.

N-Methyl- D-Aspartate (NMDA) Antagonists

A considerable body of experimental literature exists that suggests that the NMDA receptor is paramount to the establishment and perpetuation of central sensitization, and thus the development of hyperalgesia and allodynia, in chronic neuropathic pain syndromes. Drugs that possess activity that antagonizes the NMDA receptor, such as amantadine and ketamine, therefore may be beneficial in the treatment of neuropathic pain by dampening or "winding-down" central sensitization. Amantadine has been used by the author effectively in some cases of chronic neuropathic pain (3–6 mg/kg PO q 24 hours), with minimal side effects (diarrhea and excitement).

Anticonvulsants

Multiple anticonvulsant drugs have been used for the treatment of neuropathic pain in humans, including gabapentin (and its newer generation cousins), phenytoin, zonisamide, and carbamazepine. Gabapentin has been extensively studied in humans and is efficacious for the management of neuropathic pain. Gabapentin exerts in action at least partially through antagonism of α-2-δ subunits of neuronal voltage dependent calcium channels, which modulate transmission of nociception within the central nervous system. Although gabapentin has been widely used for some time in veterinary medicine, there are no published reports of its usage in the treatment of neuropathic pain. The author has used gabapentin safely and effectively in both selected cases of canine (5–10 mg/kg PO q 12 hours) and feline neuropathic pain in combination with other agents. Gabapentin use can occasionally result in sedation. Zonisamide may also prove to be efficacious in the management of veterinary neuropathic pain syndromes.

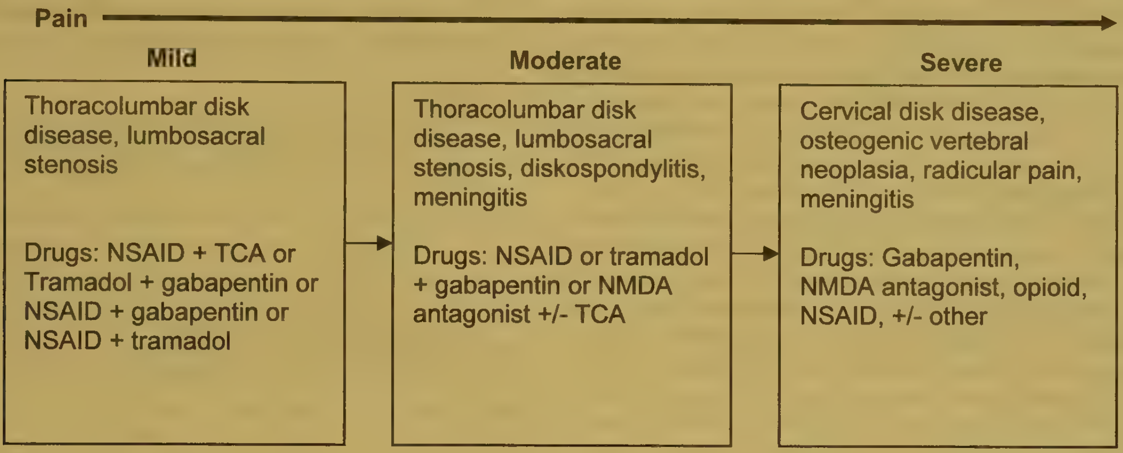
Pain
Mild
Moderate
Severe
Thoracolumbar disk disease, lumbosacral stenosis
Drugs: NSAID + TCA or Tramadol + gabapentin or NSAID + gabapentin or NSAID + tramadol
Thoracolumbar disk disease, lumbosacral stenosis, diskospondylitis, meningitis
Drugs: NSAID or tramadol + gabapentin or NMDA antagonist +/- TCA
Cervical disk disease, osteogenic vertebral neoplasia, radicular pain, meningitis
Drugs: Gabapentin, NMDA antagonist, opioid, NSAID, +/- other

Figure 1. Neuropathic Pain Treatment Approach

Table 1. Selected Drugs Used in Management of Neuropathic Pain

Drug	**Canine Dosage**	**Feline Dosage**	**Mechanisms**
Acetaminophen	10–15 mg/kg PO BID	Contraindicated	CNS COX-3 inhibition?
Acetaminophen/codeine	1–2 mg/kg codeine PO BID	Contraindicated	CNS COX-3 inhibition?
Tramadol	2–5 mg/kg PO q 6–12 hrs	1–4 mg/kg PO q 12 hrs	mu-receptor agonist Spinal serotonergic activation
Gabapentin	5–10 mg/kg PO q 12 hrs	2–10 mg/kg PO q 12 hrs	Anticonvulsant Neuronal calcium channel antagonist
Amantadine	3–6 mg/kg PO q 24 hrs	3–4 mg/kg PO q 24 hrs	NMDA antagonist May see GI side effects (esp cats)
Amitriptyline	1–2 mg/kg PO q 12-24 hrs	1–2 mg/kg PO q 24 hrs (at night)	Tricyclic antidepressant
Clomipramine	1–3 mg/kg PO 24 hrs (at night)	0.5–1 mg/kg PO q 24 hrs (at night)	Tricyclic antidepressant
Zonisamide	5 mg/kg PO q 12 hrs	Unknown	Neuronal sodium and calcium channel antagonist

Tricyclic Antidepressants (TCA)

The caudal brainstem contains the origins of multiple, descending serotonergic and noradrenergic pathways that function to endogenously inhibit transmission and projection of pain within the spinal cord. Several TCAs, such as amitriptyline, imipramine, fluoxetine, and clomipramine have been used in people for years in the treatment of chronic pain. TCAs function through the variable and in some cases selective inhibition of the reuptake of monoamine neurotransmitters, and thus facilitate endogenous descending analgesic mechanisms.

Mixed Action Analgesics

Tramadol (2–5 mg/kg PO q 6–12 hours) is the prototypical drug in this class, displaying weak binding affinity for mu-opioid receptors as well as possibly activating monoaminergic spinal inhibition of pain. Although no veterinary studies investigating the efficacy of tramadol for neuropathic pain currently exist, tramadol has been shown to be safe and efficacious in the multimodality treatment of canine osteoarthritis.

NSAIDs and Opioids

Evidence exists in humans that both of these classes of drugs are minimally efficacious for the treatment of neuropathic pain. However, considering that NSAIDs and opioids modulate pain through multiple mechanisms at multiple locations in the nociceptive pathway, and have been demonstrated to be efficacious in the treatment of other types of chronic pain, therapeutic trials with these drugs certainly are indicated in veterinary patients with neuropathic pain. In addition, depending on the specific etiology of the pain, inhibition of cyclo-oxygenase (COX) with NSAIDs may provide additional potential therapeutic benefits in individual patients (ie, COX-2 inhibition may also have some direct antineoplastic effects). The efficacy and pharmacokinetics of oral opioid formulations are largely unknown in veterinary medicine, and the author has found the efficacy of most oral opioid formulations largely unpredictable in individual patients with neuropathic pain.

In the experience of the author, combination products containing acetaminophen and codeine provide the most consistent analgesia in dogs with chronic neuropathic pain. Although technically not considered an NSAID, acetaminophen may function by acting on the COX-3 enzyme in CNS tissues. When using chronically in dogs, acetaminophen is dosed at 10 mg/kg PO BID. The dose of combination acetaminophen/codeine products should be targeted to achieve 1 to 2 mg/kg of codeine PO BID.

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THE LARGEST ENDOCRINE ORGAN — "I CAN RESIST ANYTHING BUT TEMPTATION"

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FAT AS AN ENDOCRINE ORGAN

The past decade has seen a revolution in our understanding of adipose tissue, but the revolution has been below the radar screen for most people. The functions of fat have traditionally been understood as energy storage, thermal insulation, and structural support for some organs. It is now known that adipose tissue is very metabolically active and constitutes the largest endocrine organ in the body. As we are all painfully aware, adipose tissue is the only organ with unlimited growth potential at any stage of life. We have appreciated for a long time that excess adipose tissue predisposes toward the development of insulin resistance. Recognizing that adipose tissue is not inert has helped us understand the complex relationship between obesity and some of the diseases associated with obesity, particularly so-called metabolic syndrome in humans. Doctors have talked about this constellation of risk factors for years and have called it many names, including syndrome X and insulin resistance syndrome. Metabolic syndrome is a cluster of conditions that occur together, increasing the patient's risk for heart disease, stroke and diabetes. Having just one of these conditions— increased blood pressure, increased insulin concentrations, excess body fat around the waist, or abnormal cholesterol levels—contributes to the risk of serious disease. In combination, the risk is even greater. As the name suggests, metabolic syndrome is tied to the body's metabolism, most directly to insulin resistance.

It is relatively intuitive to understand that obesity can cause mechanical stress resulting in joint injury and exacerbating chronic degenerative joint disease. The relationship to other types of diseases is less easily understood. For example, how does obesity cause Type 2 diabetes mellitus? The link is communication between fat depots and the rest of the body. This occurs via a group of proteins, collectively called adipokines, which are secreted by adipose tissue and adipose-resident macrophages and fibrocytes. Leptin, adiponectin, resistin, visfatin, retinol-binding protein, and tumor necrosis factor-alpha (TNFα) are some of the main adipokines of research interest. Enzymes such as lipoprotein lipase are also abundantly produced and released from adipose tissue. Finally, many pro-inflammatory cytokines and acute-phase proteins originate in adipocytes. Adipokines exert their effects in the central nervous system and peripherally, in tissues such as skeletal muscle and the liver.

In 1995, leptin was identified as the fat cell-specific secretory factor that mediates the hormonal axis between fat and the brain. Leptin concentrations increase with increased body fat in all species studied. Adequate energy stores are signaled by leptin and permit reproduction and normal immune function. Leptin also functions to reduce appetite. Despite high hopes that leptin would be the long-sought "lipostat," it is now known that leptin resistance develops with increasing obesity. The ability of low leptin levels to stimulate appetite is greater than the ability of high leptin levels to suppress appetite.

Adiponectin is by far the most abundant hormone present in circulation. It comprises approximately 0.01% of total plasma protein with plasma levels in the µg/ml range, whereas all other hormones, including leptin, circulate at concentrations that are at least 1000 times lower. Adiponectin is secreted exclusively by adipose tissue. When adiponectin binds to its receptors, a cascade of events lead to an increase in insulin sensitivity without stimulating insulin secretion (mainly by reduced hepatic gluconeogenesis). Adiponectin is a unique adipokine because it is inversely related to obesity; other adipokines have increased levels with increasing obesity. Since adiponectin increases insulin sensitivity, decreased adiponectin in obesity results in insulin resistance, and persistently low adiponectin levels are an important risk factor for the development of T2DM in humans. Conversely, high adiponectin concentrations protect against T2DM. Adiponectin, therefore, is thought to provide a key link between obesity and T2DM.

Feline diabetes closely resembles human T2DM including sharing many of these same risk factors: obesity, inactivity, breed (Burmese in some countries), and age (over 10). Males are predisposed.

PREVALENCE OF OBESITY IN CATS

The number of pets that are overweight or obese has reached epidemic proportions in the US and other countries. It is the leading nutritional disease in pets of western societies. There are various reports as to how common obesity is, but a large epidemiological study (a survey of pets seen in private practice) done by researchers the University of Minnesota showed that just over 35% of adult cats in the US were overweight or obese. If this population is further categorized by age, the statistic approaches 45% when cats reach middle-age (ages 10–11).

Obesity prevention in pets needs increased emphasis. First, it's easier to prevent animals from becoming overweight than it is to treat obesity. Second, significant health benefits to maintaining a normal to lean body weight have been shown in dogs and other species. Obesity prevention should be a focus of a wellness plans. Every owner should know how to do a body condition score. Most owners are unaware that neutering will reduce their pet's energy needs. The veterinary visit for spaying/neutering is an important, but often neglected, opportunity to reassess diet type and feeding management and make appropriate adjustments.

RISK FACTORS FOR OBESITY IN CATS

1. **Genetics** - Mixed breed (DSH, DLH, DMH) and Manx cats were found more likely to be obese than most purebred cats.
2. **Gender/neuter status** - Male cats are predisposed to being overweight. Neutering further increases the risk of obesity by decreasing the metabolic rate by approximately 25%. Removal of estrogens may also increase food consumption independent of the decreased metabolic rate. This may also be accompanied by an increased appetite following surgery.
3. **Age** - Risk increases with increasing age.
4. Activity- Reduced activity increases risk for weight gain.
5. **Food and feeding** - Highly palatable foods, free-choice feeding and excessive treats. In particular, feeding high-fat (premium-type foods) is associated with obesity.
6. **Other associations** - Other factors such as apartment dwelling, presumably due to decreased exercise opportunities, and an obese owner; this is "softer" data, but seems to be a commonly observed association.

Identifying obesity and determining its cause is not a diagnostic challenge. Weight gain occurs when an animal is in positive energy balance for a prolonged period of time. Energy intake increases, energy expenditure decreases, or both happen concurrently. Cats, unlike dogs, rarely suffer from endocrine diseases that cause weight gain, such as hypothyroidism. Orthopedic problems such as chronic degenerative joint disease, which is increasingly being recognized in cats, may limit the cat's ability to be active, thereby contributing to obesity.

HEALTH RISKS OF OBESITY

A recent internet-based survey of veterinarians on Veterinary Information Network (VIN) asked which diseases they think their clients associate with obesity. Most participating veterinarians believed clients associate arthritis, heart disease, and diabetes mellitus with pet obesity. Another Internet survey, conducted by Intervet, asked pet owners which diseases they associated with obesity. Interestingly, only a small percentage of clients associated *any* disease with obesity. Diseases that were associated were cancer, heart disease, and diabetes, but not arthritis, which was the #1 disease veterinarians, expected owners to answer. These results emphasize that many clients do not take pet obesity seriously, as they fail to recognize that obesity carries serious health risks in pets as it does in humans.

Many severely obese cats require surprisingly few calories for maintenance, so weight loss recommendations must be tailored to the individual. It is important to provide adequate protein while restricting energy intake. Consider options for increasing activity as well as reducing calories. In cats with concurrent diabetes mellitus and obesity, diabetes control must be closely monitored during weight loss. Expect changing insulin requirements as cats lose weight. Indicator litter (Purina® Glucotest™ brand Feline Urinary Glucose Detection System, St. Louis, MO) is a useful way to detect if the cat's insulin requirements are dropping, as some glucose should spill into the urine over the course of a week in a typical diabetic cat

Overweight cats experience many of the same health problems and risks that overweight humans do. These include: Type 2 diabetes mellitus, neoplasia, dental disease, dermatologic diseases, and lower urinary tract problems. In addition, although harder to measure, obesity exacerbates existing musculoskeletal problems and pregnancy complications, and is associated with delayed wound healing, increased anesthetic/surgical risk, and probably reduced life expectancy. As everyone who works in a veterinary clinic knows, obesity also makes tasks like collecting blood samples and placing intravenous catheters much more difficult.

WEIGHT REDUCTION

In planning a weight loss program for cats, it is important to make a conservative estimate of "ideal" body weight in order not to excessively restrict calories. In cats, excessively rapid weight loss may result in hepatic lipidosis. Do not exceed 1% body weight loss per week for cats. (In dogs, weekly weight loss of 2% is a safe target). Also, note that the new microsomal triglyceride transfer protein inhibitors, such as dirlotapide, are not approved for cats, and must not be used off-label in cats due to the high risk of hepatic lipidosis.

One equation to estimate resting energy requirement (RER) is: 30[ideal body weight in kg] +70). In order for cats to lose weight, the calculated RER is usually reduced by 20%. Note this is lower than the 30% to 40% restriction usually used for dogs due to the risk of hepatic lipidosis in obese cats if calories are restricted too severely.

Protein level in the weight loss diet is important for maintaining lean body mass during weight reduction and prevention of hepatic lipidosis. In managing a cat that is both diabetic and obese, a high-protein, low-carbohydrate diet is also helpful in control of diabetes. Be aware that even stable, long-term diabetics may experience diabetic remission as a result of weight loss and/or a change to a high-protein, low-carbohydrate diet, therefore clinical signs and blood glucose must be closely monitored during weight loss. Cats need to consume about 4 grams of protein per kg of lean (optimal) body weight per day during weight loss in order to meet their daily protein requirements and preserve lean body mass. This means that a high-protein, low-carbohydrate diet should be selected to manage both weight loss and diabetes. For an obese diabetic cat, a food with 40% to 60% protein (expressed as a % of kcal of metabolizable energy) and <30% carbohydrate would be a good choice. Intake of the conditionally essential amino acid, L-carnitine, is also important during weight loss to help ensure maintenance of lean body mass, which maintains basal metabolic rate while total body weight decreases. L-carnitine intake of at least

250 mg/cat/day should be ensured through diet selection and supplementation. For example, Hill's feline m/d (dry) and Hill's r/d (dry) supply 13 mg and 16 mg L-carnitine per 100 kcal of diet consumed, respectively. Commercial food options for weight loss and diabetes management in cats are listed in Tables 1 and 2.

Table 1. Commercial Food Options for Weight Loss in Cats*

Food	Caloric content (ME**)	Protein content (gms/100 kcal ME)	Protein (% of kcal ME)	Fat (% of kcal ME)	Carbohydrate (% of kcal ME)
Purina Veterinary Diets® OM Feline Formula (dry)	321 kcal/cup	16.5	56.2	20.5	23.3
Purina Veterinary Diets® OM Feline Formula (canned)	150 kcal/can (156 g can)	11.4	43.1	34.4	22.4
Hill's Prescription Diet® Feline r/d® (dry)	263 kcal/cup	11.4	40	24	36
Hill's Prescription Diet® Feline r/d® (canned)	116 kcal/can (156 g can)	11.4	38	25	27
ROYAL CANIN Veterinary Diet™ feline CALORIE CONTROL CC™ In Gel Can	130 kcal/can (165 g can)	11.4	45.4	46.5	8.1
ROYAL CANIN Veterinary Diet™ feline CALORIE CONTROL CC™ In Gravy Pouch	66 kcal/pouch (85 g pouch)	11.0	43.9	36	20.1
Eukanuba Restricted-Calorie™/Feline Dry Formula	271 kcal/cup	9.4	34	23	43
Eukanuba Restricted-Calorie™/Feline Canned Formula	204 kcal/can (170 g can)	9.5	40	41	19
Eukanuba Veterinary Diets Optimum Weight Control formula (dry)	357 kcal/cup	9.7	37	29	34

* Data current as of March 2006
**ME = metabolizable energy

Table 2. Commercial Food Options for Diabetes Management in Cats*

Food	Caloric content (ME**)	Protein content (gms/100 kcal ME)	Protein (% of kcal ME)	Fat (% of kcal ME)	Carbohydrate (% of kcal ME)
Hill's Prescription Diet® Feline m/d® (canned)	156 kcal/can (156 g can)	13.1	46	41	14
Hill's Prescription Diet® Feline m/d® (dry)	480 kcal/cup	12.3	43	44	13
Purina Veterinary Diets® DM Feline Formula (canned)	194 kcal/can (156 g can)	11.9	46.3	47.1	6.6
Purina Veterinary Diets® DM Feline Formula (dry)	592 kcal/cup	12.9	49.7	37.4	12.9
ROYAL CANIN Veterinary Diet$^{\text{TM/MC}}$ feline DIABETIC DS 44$^{\text{TM/MC}}$ (dry)	247 kcal/cup	12.3	47.5	27.9	24.6

* Data current as of March 2006
**ME = metabolizable energy

Steps in Formulating a Weight Loss Plan for a Diabetic Cat

1. Make conservative estimate of target body weight.
2. Calculate daily kcal needed using either 80% of current measured intake or 80% of resting energy requirement (RER) at ideal weight.
3. RER = 30[ideal body weight in kg] +70
4. Assess need for diet change. Select high protein diet and diet form (dry or canned).
5. Ensure that diet selected will provide close to 4 grams of protein per kg (at target body weight).
6. Closely monitor diabetes and progress of weight loss and reassess diet plan.

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TIPS FOR ENCOURAGING FOOD INTAKE IN HOSPITALIZED CATS

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It has been estimated that up to 50% of hospitalized small animal patients are malnourished. Malnutrition and wasting contribute to many aspects of critical illness including impaired immune function, increased susceptibility to infection, delayed wound healing, decreased strength and vigor, and increased morbidity and mortality. Indeed, malnutrition has been implicated as a significant factor that influences outcome in critically ill patients. Therefore, prevention of malnutrition by ensuring adequate nutrient intake is crucial in the management of critically ill patients. It has been well established that nutritional support in critically ill patients will decrease morbidity and mortality, improve tolerance to invasive procedures, shorten hospitalization periods, decrease incidence of infections, enable earlier ambulation, hasten wound healing, and reduce complications.

One of the key factors that veterinarians consider to ensure adequate food intake is palatability. Palatability is complex and, for hospitalized cats, essential. However, palatability is not just about flavor enhancers. Rather it involves three essential components: the cat (species and individual), the environment, and the food (smell, shape, texture, taste, nutritional composition). Food selection in cats is influenced by factors such as evolutionary palatability factors, natural feeding behavior (neophilia, neophobia), and learned feeding behavior (maternal influence and dietary history). Exploring and understanding each of these factors can provide insight into how to encourage food intake in hospitalized cats.

The feeding behavior of wild cats can help to explain the feeding behavior of domesticated cats. Cats are solitary hunters, capturing small prey, which they eat alone. They eat a large number of meals each day and they eat day and night. Therefore, in the hospitalized environment, providing fresh meals multiple times during the day and night may facilitate food intake.

The behavior of cats in selecting their food is extremely variable. In a situation where they must make a choice, cats rely on their senses to evaluate food. When the smell of one of the foods appeals to a cat, it will eat only that food. When the smell of both foods is found appealing, the cat tends to eat both and make a choice based on taste and how the food feels inside the mouth. In addition to these purely sensory considerations, cats may or may not recognize the food on the basis of past experience. According to the foods available and their knowledge of food, cats choose through different strategies: neophilia, neophobia, or aversion.

Neophilia is preference for a food never encountered by the cat or food that has not been recently been encountered. This behavior is quite common in carnivores and has been identified in cats. The intensity of neophilic behavior depends on the foods' relative palatability. If the new food is less palatable than the usual food, the effect is short-lived. Obviously, if the new food is more palatable than the usual food, the neophilic effect will be more pronounced and persistent.

Neophobia corresponds to avoidance of a new food compared with the usual food. It is also called "fixation of food habits." In the wild, carnivores, unlike omnivores, display more neophilic than neophobic behavior (Thorne, 1982). Neophobia is more common when meals are served in unusual conditions[8] or if the animal is under stress.[3] Therefore introducing a new diet under unusual circumstances such as when a cat is stressed (by pain or illness, by being away from its owner, in a veterinary clinic, etc.) is more likely to result in neophobia than if the new food is introduced under familiar, positive circumstances. Always introduce a new diet under the least stressful conditions for the cat. The more regular the diet, the more persistent the neophobia. A few days are required to overcome neophobia and for a cat to experiment with the new food.[5] To overcome neophobia toward a new flavor, cats should not be exposed to the smell alone; they must also taste it.[4] Gradual diet transitions are always recommended to minimize any potential gastrointestinal upset to the new diet. In addition, diet transitions are an excellent method to overcome neophobia.

There are several approaches that can be used to help overcome neophobia. Offer the new diet each day for at least 3 days (offering fresh food each time). Persistent exposure, even if the cat initially refuses the new food, may help overcome neophobia. Bradshaw showed that neophobia disappeared after the third day of presentation of food flavored with lamb.[4] Try putting a small piece of the new food in the cat's mouth, so that the cat tastes the new food. If the diet is a wet food (can or pouch), try smearing a little of the food onto the pet's front legs. Most pets will lick off the food and this can habituate the pet to a new food. Mix a little of the new canned food into the cat's drinking water to help habituate the cat to the new taste. Note, however, that some cats have particularly requirements for clear, clean fresh water, and not all cats will appreciate wet food in their water.

When smell or food is associated with positive consequences, the food will be eaten again. Conversely, if the smell or food is associated with distress, an unpleasant experience (hospitalization) or digestive problem (poisoning), the food will be avoided in the future. This phenomenon is known as **aversion.**[5] Aversion is a strategy used by animals to avoid foods that are unsuitable for them. It is a form of negative conditioning. In cats, aversion sets in very quickly. A single meal associated with unpleasantness leads to a refusal to eat. Such aversion can persist for 40 days[2] or more.[6] The smell alone of a food associated with digestive disorders is enough to elicit aversion. Cats even go so far as to show aversion for their usual food if it is served in the presence of an air current bearing the odor of a food to which they have developed an aversion.[6] Therefore, it is important to be careful when preparing foods for cats at the hospital. Odors may travel and could trigger an aversion reaction even in cats being fed their usual diet. It is best to prepare the cats' food in a place where food odors cannot reach the cats.

Cats need to feel safe and secure within their environment. To this end veterinarians and owners need to provide facilities for the main behavioral functions of eating, sleeping, and playing and also ensure that the cat has the ability to control its own stress through the natural mechanisms of hiding and retreating. One of the problems with hospitalization is that the cat finds itself constantly on display and correspondingly vulnerable. Taking steps to provide the cat with a constant and predictable environment, both in terms of physical structure and scent profiles, will help to increase the cat's security; while the provision of access to high up resting platforms, secure bolt holes and hideaways will decrease the use of oral appeasing behaviors, such as over grooming. Hospitalized cats may be uncomfortable eating because of the lack of space results in the spatial requirements of cats being disrespected. Moving the cats to larger dog cages, which permits the separation of food, lodging, and litter, may restore the appetite of some cats.

Dietary history can play a role in determining food preferences. This is true for cats raised in different circumstances, but may also apply to pets raised in similar conditions. Five different foods (canned meat, canned fish, raw beef, cooked beef, dry food) were offered in a series of two-bowl tests to 64 cats, 28 living in homes and 36 living freely on farms. The housecats showed a much stronger preference for dry food. Conversely, while the housecats were barely attracted by the raw beef, it was the farm cats' favorite food.[1] Way of life and prior dietary experience explain the differences in dietary preferences between these two groups of cats. A cat's gustatory system is functional in the final days of gestation.[9] Therefore, the acquisition of certain preferences may occur as early as during gestation. Weaning is also crucial. When eating their first solid food, kittens do not choose the most palatable food according to innate criteria. They choose what their mothers eat, even if this food is unusual for cats.[11] Dietary preferences are not innate; they are acquired through social influences after birth.[10]

Food characteristics and the cat's perception of these characteristics also influence a cat's food choices. Food selection by the cat involves several sequential steps: First, the cat will *smell* the food, assessing the food's aroma and temperature. Basic olfactory acuity increases when the animal is hungry and drops with satiation. With age, smell is the first sense to decline. Senior pets may eat less as their sense of smell deteriorates. Many drugs also disrupt the sense of smell. Cats prefer food at near body temperature. This corresponds to the temperature of prey caught in the wild.[7] They are less attracted to foods at room temperature or colder, as when taken straight from the refrigerator. As well, foods heated above body temperature are also less appealing, with a rather dramatic increase in refusal rate of foods above 104°F (40°C).

If the aroma is appealing, the cat will then attempt to pick up the food, assessing the ease of *prehension* (grasping by the mouth). Once the food is in the cat's mouth, the cat will assess the *taste* as well as the *physical properties* of the food, ie, the *feel* of the kibble in his mouth, how easy it is to break and chew the food, the size and shape of the kibble. There are five universally recognized tastes: acid, salty, bitter, sweet, and unami. Cats are particularly sensitive to bitter taste and detect it at very lower concentrations. They do not respond to sweet taste. Cats are particularly attracted to strong acid taste. Taste sensitivity declines with age. Some diseases and drugs affect taste, eg, thyroid dysfunction, chronic renal insufficiency, and diabetes mellitus. Factors including ingredients (selection and quality), manufacturing practices, pet food preservation systems, palatability enhancers, storage, and handling systems maximize the taste appeal of a food.

Pet food formulation is only one component of palatability. Aroma, ease of prehension, taste, kibble size, shape, density and texture, manufacturing practices, quality assurance practices, and packaging technology all affect food acceptance. Species evolution affects cat feeding behavior and this must be understood and taken into account when encouraging hospitalized cats to eat.

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FEEDING TUBES FOR ENTERAL NUTRITION

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METABOLISM OF THE TRAUMATIZED PATIENT

Tissue trauma, sepsis, burns, and major surgery all induce major metabolic changes within the small animal patient. With each of these stresses the animal's basic metabolic rate is accelerated and protein catabolism occurs leading to a potential state of negative nitrogen balance. The metabolic response to injury is an adaptive mechanism whereby the body mobilizes and accelerates immune defense and wound repair mechanisms in the face of little or no nutritional intake. This metabolic response to injury is in contrast to starvation whereby the body lowers its metabolic rate and nitrogen loss to conserve body resources.

Protein-calorie malnutrition (PCM) occurs when the metabolic response to injury becomes prolonged due to the severity of the injury or because of a hypermetabolic state such as that caused by sepsis. When protein-calorie malnutrition is present cell-mediated immunity is impaired, there is a higher risk of infection, wound healing may be impaired, anemia and hypoproteinemia may occur, generalized muscle weakness may be present, and multiple organ dysfunction leading to death may occur. It may take only 5 to 10 days of anorexia to compromise the immune system and deplete the body's muscular glycogen stores. Without adequate nutrition during this period, humoral and cellular immunodeficiency occurs and animals frequently die despite the use of aggressive antibiotic therapy.

Most anorexic animals who are too weak or sick to eat still have a gastrointestinal tract that is capable of sufficient digestion and absorption of nutrients. This is especially true in the small intestine. Enteral alimentation offers the clinician an alternative to parenteral (intravenous) nutrition when normal ingestion of food is not possible. Enteral nutrition is both practical and easy to perform and not fraught with the expense and serious complications often seen with parenteral nutrition. The goal of enteral alimentation is to provide calories and protein sufficient to achieve a positive calorie and nitrogen balance in a safe and convenient manner.

INDICATIONS

Enteral feeding is indicated in those patients in which anorexia is present and evidence of protein-energy malnutrition is present prior to surgery. In animals in which the stomach is functioning, feeding can be accomplished through the use of **nasogastric**, **esophagostomy**, or **gastrostomy** tubes. Nasogastric tubes are small bore (3.5–8 Fr) usually necessitating a liquid diet whereas esophagus or gastrostomy tubes are often larger (14–20 Fr) and a blended gruel of the animal's regular food can often be fed through the tube. It is, however, important to strain the food prior to injecting it, since one small clump of food may plug the system. With the esophagostomy or gastric tube the animal's daily caloric needs can usually be met by dividing the feedings into 2- to 6-hour intervals. It is especially important to feed slowly through a esophagostomy tube because the possibility for regurgitation and aspiration does exist. In those patients in which the stomach is not functioning or needs to be bypassed after surgery, the use of **enterostomy tubes** or **needle catheter jejunostomy** is an effective way of feeding. Fluids, electrolytes, and oral medications can also be administered through these tubes if necessary.

Placement of enterostomy catheters should be considered in those patients 1) that have an acute weight loss of 10% body weight or chronic weight loss of 15% to 20% body weight, 2) are hypoproteinemic, 3) are septic, 4) in gastric or pyloric resections, 5) in extra-hepatic biliary diversions, 6) in multiple enterotomy or massive intestinal resections, 7) in any condition where chronic cachexia may adversely affect wound healing or 8) in animals with unresponsive pancreatitis. Studies show that immunocompetence returns within as few as 48 hours after hyperalimentation. If the surgeon anticipates that oral feeding might be delayed or that hypermetabolic complications might be present, the tube should be placed at the time of surgery. These tubes are easily removed but difficult to place after surgery.

SURGICAL TECHNIQUES

Nasogastric Tube

This method of feeding is commonly used in cats and will also be tolerated by dogs. Lidocaine 2% is instilled down the nostril and a lubricated 3.5–5.0 Fr (cats) or 8 Fr (dogs) polyvinyl feeding tube is passed in a ventromedial direction through the ventral meatus of the nose. The tip of the tube is passed into the distal esophagus. Passage into the stomach may result in reflux esophagitis. Radiographs can be taken to determine the tube location. The end of the tube is then affixed to the cat's face with sutures. An Elizabethan collar is applied. The tube is capped. Feeding can be performed through intermittent bolus injections of 10 mL/kg or using a slow infusion of 2–4 mg/kg/hr.

Pharyngostomy Tube

The original technique suggested that the tube be placed rostral to the hyoid apparatus but aspiration pneumonia and airway obstruction resulted because of interference with the glottis, particularly in cats. Now it is recommended that the tube be introduced distal to the hyoid apparatus. A 10–16 Fr tube can be used in cats and a 16–24 Fr tube for dogs. Pharyngostomy tubes have **fallen out of favor** because of more complications in comparison to esophagostomy tubes.

Esophagostomy Tube

This method has been recently described and apparently eliminates much of the potential for airway obstruction and aspiration pneumonia. The tube is inserted using a curved Carmalt or Mixter right angle forceps. The forceps are advanced 3 to 4 cm past the larynx and then a stab incision is made over the intranasal. The tip of the catheter is then advanced into the lumen of the esophagus and either normograded directly down the esophagus or pulled back into the mouth, reversed, and then inserted down the esophagus. The tube should be premeasured up to the level of the 10th rib to make sure it does not enter the stomach. A 14 to 16 Fr catheter is commonly used in cats and 18 to 20 Fr for dogs.

Gastrostomy Tubes

Gastrostomy tubes can be placed through an **open** operative technique or via a **percutaneous** technique using either an endoscope (PEG tube) or nonendoscopic method using an Eld cannula (PNG tube). With the **open technique** a ventral midline approach is made and the stomach is exteriorized. A double purse-string suture is placed and a 16 to 22 Fr Foley catheter is introduced through the left flank and placed into the stomach lumen. The purse-string sutures are tightened and invert the stomach around the tube. Four simple interrupted preplaced sutures are used to draw the stomach to the oblique muscles and the balloon is inflated. With slight traction on the catheter, the sutures are tied. Omentum is wrapped around the gastrostomy site. The subcutis and skin are closed and the catheter is fixed to the skin using a Chinese finger snare suture.

With the **percutaneous endoscopic gastrostomy** (PEG) the patient is positioned with the left side up and the stomach is insufflated. A Bard or Pezzer mushroom-tipped catheter is drawn "inside-out" by tying it to a piece of suture material which has been passed into the stomach lumen percutaneously through an intravenous (IV) catheter and retrieved using an endoscope. Traction is placed on the catheter to keep the stomach wall against the peritoneum and prevent leakage. With the **percutaneous nonendoscopic gastrostomy** an Eld cannula is inserted through the oral cavity and into the stomach. The curved portion of the cannula is tipped up against the left body wall behind the 13th rib and the sharp stylet is pushed through the stomach and body wall. A piece of suture material is tied through the hole in the stylet and the cannula is retrieved out through the oral cavity. The mushroom catheter is then affixed to the suture and the remainder of the procedure is exactly like the PEG tube placement.

LOW-PROFILE GASTROSTOMY BUTTON

Some patients require long-term or even permanent gastrostomy tube placement for conditions such as esophageal neoplasia, strictures, megaesophagus, or as an aid to malnutrition caused by cancer or chronic renal failure. These patients may benefit greatly from the use of commercial low-profile feeding devices such as the Passport[7] (Passport-Global Veterinary, New Buffalo, MI) or Surgitek One Step Button[7] (One StepJ-Surgitek, Racine, WI). The Passport button has a one way valve that is convenient to use. It is made to be used as a replacement unit for a standard mushroom catheter. When the old mushroom catheter is pulled, the new unit is put in its place by merely collapsing the mushroom of the new unit with a stylet and gently inserting it into the old stoma. The one step button is placed exactly like a mushroom PEG tube, but once the unit is in place an outer wrapper comes off the guide tube and two side flanges, one with an attached stopper plug, are left. The disadvantage of the Surgitek button is there is no valve and food spillage is more common.

JEJUNOSTOMY TUBE

A loop of distal duodenum or proximal jejunum distal to the surgery site is isolated and a purse-string suture using 3-0 or 4-0 suture material is placed on the antimesenteric border. A commercially available Kendall Argyle feeding jejunostomy tube (Tyco Healthcare), a 3 to 5 Fr Kendal Sovereign urinary catheter (Tyco Healthcare) (introduced through a 12- to 14-gauge needle) or a 16-gauge through-the-needle polyvinyl catheter (Intra Cath, CR Bard, Inc.) is passed through the abdominal wall 4 to 5 cm from the midline. The needle is then inserted through the intestinal purse-string suture and tunneled subserosally 1 to 2 cm before entering the intestinal lumen. The catheter is advanced aborally in the lumen for a distance of 20 to 25 cm, the needle is withdrawn, and the purse-string suture tied. The enterostomy site is fixed to the abdominal wall using 4 to 6 preplaced sutures or a simple continuous pattern of 4-0 monofilament suture material. The catheter is then fixed to the skin using a finger trap suture or tape. An extension tube is attached and abdominal dressings are applied.

CALORIC REQUIREMENTS

The following chart describes the formula used by the author for estimating caloric needs (Table 1). It must be remembered that basal caloric requirements increase by 50% to 150% depending on the degree of hypermetabolism.

Protein requirements are estimated at 4.4 to 8.8 g/kg body weightfor dogs and are probably slightly higher for cats. The protein content of most commercial liquid diets ranges from 16% to 20%. This is based on a current recommendation for people that 16% of available calories be provided by protein. This value is probably lower than ideal for use in dogs and cats.

Table 1. Caloric Needs Estimation Chart

	Basal Needs (kcal/kg)	Major Surgery (kcal/kg)	Polytrauma/Burns/Sepsis (kcal/kg)
Cat	75	110	150–190
Dog, 1–10 kg	70–80	100–120	160–200
Dog, 10–20 kg	60–70	90–110	140–180
Dog, >20 kg	50–60	75–90	120–160

DIETS

There are two basic types of diets available for enteral tube feeding, polymeric and monomeric. **Polymeric diets** are composed primarily of polypeptides and polysaccharides (starches). They require **digestion** as well as **absorption**. The advantage of these diets is that they have low osmolality (350–450 mOsm/L) and therefore are less likely to promote osmotic diarrhea. Polymeric diets are cost effective and are good for use in most standard enteral hyperalimentation regimes. Polymeric diets used at the University of Florida include Isocal (Mead Johnson), Ensure (Ross Labs), and Pulmocare (Ross Labs). These diets have low osmolality and contain approximately 16% protein. Ensure and Isocal has a caloric density of 1 kcal/mL while Pulmocare has a density of 1.5 kcal/mL. Diet higher in protein are the Clinicare Diets produced by Ag Vet. These liquid diets are specifically formulated for dog (24%) and cat (28%) protein needs.

Monomeric diets are elemental diets composed of amino acids and monosaccharides with a minimal amount of fat content. The diets require minimal to no digestion and are absorbed over as little as 100 cm of bowel. They are hypoallergenic and have a low residue. Unfortunately, they are hyperosmolar (600–800 mOsm/L) and often cause diarrhea. Additionally, they are relatively expensive. Monomeric diets are usually reserved for use in patients with significant intestinal tract disease. They are indicated for use in malabsorption syndromes or when short bowel disease is present. Examples of monomeric diets are Vital (Ross Labs) and Vivonex (Norwich Eaton). These diets are approximately 16% protein and have a caloric density of 1 kcal/mL.

ADMINISTRATION AND COMPLICATIONS

With esophagostomy or gastrostomy tubes feed no more than 30 mL/kg of body weight with each feeding. The liquid diets can be divided and injected in bolus form every 6 hours or they can be given at a slow continuous infusion of 5–10 mL/kg/hr. The main complications associated with enteral hyperalimentation are osmotic diarrhea, and hyperglycemia. Osmotic diarrhea can usually be avoided by diluting the liquid diet with water by 50% on the first day and feeding only the calculated volume. The concentrations and volumes are then gradually increased to that and by day 4 or 5 the concentrated diet at full volume can be fed. Hyperglycemia can often be controlled by slowing the diet administration rate. An example of a starting regimen is as follows:

Day	Volume	Concentration
1	50%	50%
2	75%	50%
3	75%	75%
4	100%	100%

Contraindications to the use of enteral hyperalimentation include adynamic ileus of the intestinal tract and persistent diarrhea that is not controlled by administration rate or drugs.

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CRITICAL CARE NUTRITION

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The beneficial effects derived from the nutritional support of diseased human patients and experimental animal models include enhanced immune function, wound repair, an accelerated response to therapy, quicker recovery times, and increased survival. Despite these benefits, the nutritional needs of hospitalized patients are often ignored. In addition, the nutritional needs of critically ill patients are largely forgotten due to the intense focus on life-threatening medical and surgical problems. The goal of nutritional support is to provide a formula of nutrients in proportions that can be utilized by the patient with maximal efficiency.

Malnutrition is probably more common in veterinary patients than is recognized. Malnutrition is an unbalanced intake of protein and/or calories to support tissue metabolism and has the potential to undermine proper medical or surgical therapeutic management of a hospital case. Most veterinary patients are likely to be deficient in both protein and calories due to a decrease in food intake. At first glance patients resting in a cage may appear to require little or no nutrition, when in fact their needs are significant.

Survival rates in humans have been directly correlated with available muscle mass. Loss of more than 25% to 30% of body protein compromises the immune system and muscle strength, death results from infection, pulmonary failure, or both.[2] The benefits of nutritional support are many and include increased immune function, increased wound healing, increased response to therapy, shortened recovery times, increased survival rates, and lower hospitalization costs.

A recent publication estimated the proportion of hospitalized canine patients in a negative energy balance. The study related calories consumed in the hospital to appetite at home following discharge, in order to determine why dogs were in a negative-energy balance and the assess the relationship between body condition score (BCS), physical status score (PSS), diagnosis, and caloric intake with patient outcome. The study was conducted at three veterinary referral hospitals across the country. Overall, daily feeding data and outcomes for 276 dogs over 821 days in the hospital were evaluated. In only 27% of those days was a positive energy balance obtained (> 95% RER [resting energy requirement]). Eighty-three percent of the dogs were considered to have returned to a normal appetite within 2 days of being discharged. Of the 821 dogs days analyzed, 601 were determined to be in a negative energy balance. This was attributed to several factors: 22% due to poorly written orders, 34% due to orders to withhold food, and 44% of the dogs refused to eat. Overall, caloric intake had a significant, positive effect on patient outcome. Although an equivalent study has not been done in cats, one might predict similar findings.

INDICATIONS FOR NUTRITIONAL SUPPORT

As a starting point, animals that have been anorectic for >5 days or that have lost >10% of their body weight should be considered for nutritional support. In addition, patients that are hypoalbuminemic, have a condition with increased energy demands, or one with excessive nutrient losses also warrant nutritional support.

PATIENT EVALUATION

Assess Nutritional Status

Obtain a complete diet history (including supplement use, diet consumed, and caloric intake), a physical examination, and appropriate laboratory work. A body weight and body condition score should always be obtained for every patient, but it is important to realize its limitations. Remember that body weight does not differentiate fat, lean tissue, and water.

Determine Caloric Needs

There is a paucity of data on the energy requirements of sick animals. Current thinking among veterinary nutritionists is that every patient should consume *at least* enough calories to meet their daily resting energy requirements. Similarly, most sick or hospitalized cats are inactive and therefore do not have normal maintenance energy requirements (MER). It is likely that the true energy needs of most hospitalized patients fall somewhere between RER and MER. In human patients, some disease states result in higher than normal maintenance energy needs (hypermetabolism). However, energy requirements for various disease states in cats are unknown and extrapolation from other species may have detrimental effects, as overfeeding can be as harmful as inadequate nutrition. Close observation of the patient with respect to body weight changes, ongoing losses, and exam findings will help determine whether to increase the patient's caloric intake towards MER or to remain at RER, respectively. Importantly, it should be standard protocol to calculate a patient's energy requirements and record food intake on a daily basis to determine the adequacy of caloric intake and the need for nutritional support.

Accordingly, the author recommends that initial calculation of energy requirements be based on the following equations. Importantly, it should be standard protocol to calculate a patient's energy requirements and record food intake on a daily basis to determine the adequacy of caloric intake and the need for nutritional support.

A linear formula can be applied to determine the RER of patients weighing at least 2 kg. Alternatively, one can utilize an allometric formula that can be applied to all cats, as well as those weighing <2 kg.

Linear formula (body weight $\geq$ 2kg):

$$\text{RER (kcal/day)} = (30 \times \text{BW}_{\text{kg}}) + 70$$

Allometric formula (body weight <2 kg):

$$\text{RER (kcal/day)} = 70\ (\text{Bw}_{\text{kg}}{}^{0.75})$$

The veterinary literature reports various values or factors to multiple the RER by to determine the patient's final caloric requirement. This practice should be used with caution because the ability to discriminate between a patient requiring 1.2 and 1.5 times the RER is virtually impossible. It is important to remember that every equation has a potential error rate of approximately +/– 25%. This author in most instances begins by feeding RER and then monitoring and adjusting as needed.

DIETARY CHARACTERISTICS

Ideally, critical care diets should be highly digestible, highly palatable, and energy dense.

Fat

High-fat diets, as a rule, are usually well accepted and tolerated. Fat provides at least twice as many calories per unit of volume, thereby enabling an increased caloric consumption in patients with limited food intake. Although fat can increase the palatability and the initial acceptance of a diet, it is the authors' experience that sudden increases in dietary fat appear to be one of the most consistent and least recognized causes of gastrointestinal distress, especially pancreatitis. Slowly introducing a new diet can help prevent this problem. Fat also helps to decrease the osmolarity of the diet which may help reduce diarrhea with feeding.

Protein

Critically ill animals often exhibit protein malnutrition due to increased protein catabolism, negative nitrogen balance and ongoing nitrogen losses. Highly digestible proteins of a high biological value should be used. Protein quality is dependent on protein digestibility, bioavailability and its amino acid composition. In some cases, protein concentration may need to be restricted in cats with renal insufficiency and certain liver diseases.

Taurine is an essential amino acid in cats. Arginine is another required amino acid in all cats. In illness, protein turnover is increased and additional arginine may be necessary for the urea cycle to continue functioning. Arginine also has a role in wound healing, cell-mediated immunity, nitrogen balance, release of insulin, and as a precursor to nitric oxide. Most human enteral products are deficient in arginine as well as taurine.

Glutamine is the preferred energy source of rapidly dividing cells such as enterocytes and immune cells and conditionally essential in under some conditions. Glutamine is rarely found in human enteral diets because of its instability.

Other Characteristics

Enteral diets are classified as monomeric (elemental) or polymeric. Monomeric diets do not require digestion prior to absorption. Currently there are no veterinary monomeric diets. Disadvantages of these diets are expense, poor palatability, and diarrhea. Occasionally the use of a human elemental diet may be indicated in the cat. However, these diets do not contain enough protein to meet the cat's requirement over the long term, so if their use is indicated in a feline patient, additional protein, taurine, and possibly arginine will need to be added.

All commercial veterinary diets are polymeric diets (contain intact protein, polysaccharides and long chain triglycerides). These diets require digestion and tend to be iso-osmolar and palatable.

SELECT A ROUTE OF ADMINISTRATION

Oral or enteral feeding is the preferred route because it is the safest, simplest, cost effective, and is the most physiological. Some patients may consume their food voluntarily, but most critically ill patients are unlikely to consume enough calories to meet their needs. It then becomes the clinician's challenge to determine they best approach to feeding. The remaining options include force feeding, the administration of appetite stimulants or assisted feeding by an enteral feeding tube or by parenteral nutrition.

Appetite stimulants have been used mostly in cats with partial anorexia. In this author's opinion appetite stimulants are of little value because although they may encourage the animal to eat a few bites, they rarely eat enough to meet even their resting energy requirements. Force-feeding is not advised because it is very difficult to meet the animal's resting energy requirements and is very stressful to the patient and those working with the animal. Furthermore, many animals will develop a learned aversion to foods fed by this method, as they will associate the food with the negative experience of being force fed.

ENTERAL FEEDING ACCESS DEVICES

Most feeding tubes used today are made of polyurethane or silicone. These materials are replacing the older polyvinylchloride feeding tubes that tend to stiffen when exposed to digestive juices and are more irritating to patients, necessitating frequent tube replacement. Silicone is softer, more flexible and has a greater tendency to stretch and collapse. Polyurethane is stronger than silicone, allowing for a tube of this material to have thinner walls and thus a larger internal diameter, despite the same French size. The flexibility and decreased internal diameter of silicone tubes may lead to clogging or kinking of the tube. Both polyurethane and silicone do not breakdown readily, providing a longer lifespan. The French (F) unit measures the outer lumen diameter of a tube (each French unit is equal to 0.33 mm). Tubes that are too flexible may be chilled before placement to increase stiffness.

Nasoesophageal—A good choice for the short-term (less than 10 days) nutritional support of most patients that have a normal nasal cavity, pharynx, esophagus, and stomach. Nasoesophageal tube feeding is contraindicated in animals that are vomiting, comatose, or lack a gag reflex. Polyvinylchloride or red rubber tubes are the least expensive tubes for cats, although the polyvinylchloride tubes may harden within 2 weeks of insertion and cause irritation or ulceration of the pharynx or esophagus. Tubes made of polyurethane or silicone are more expensive; however, they are less irritating and more resistant to gastric acid, allowing prolonged usage. A 5 or 6 French x 36-inch tube is recommended for cats.

The most common complications include epistaxis, dacrocystitis, rhinitis, tracheal intubation, and secondary pneumonia, and vomiting. Pneumothorax secondary to nasopleural intubation and esophagitis with stricture formation are less common serious complications. The risk of tracheal intubation can be minimized by verifying the position of the feeding tube before securing and before each feeding.

A major disadvantage of nasoesophageal feeding tubes is their small diameter, necessitating the use of liquid enteral formulas. Commercially available canned pet foods that are diluted with water will invariably clog the feeding tube. The caloric density of most human and veterinary liquid enteral formulas varies from 1.0 to 1.5 kcal/mL. Diets are fed full strength on continuous (pump infusion) or bolus feeding schedules.

Pharyngostomy—This approach has become virtually obsolete with the advent of percutaneous gastrostomy and esophagostomy tube placement. Pharyngostomy requires general anesthesia and meticulous attention when being placed to avoid interference of epiglottic movement and partial obstruction of the larynx.

Esophagostomy—These tubes are easily inserted, and insertion only requires light general anesthesia or heavy sedation. The only major complication that has been associated with esophagostomy tube placement is wound infection at the ostomy site where the tube exits the skin. Daily meticulous care of the ostomy site has been effective in preventing infection.

Gastrostomy—Requires general anesthesia, with placement of the tube via percutaneous placement or during laparotomy. This procedure enables one to place relatively large-diameter catheters into the patient's stomach, with most cats tolerating 20 French tubes. Tube migration and inadvertent tube removal can occur with subsequent peritonitis or subcutaneous cellulitis development.

Jejunostomy—Requires general anesthesia; however, new methods have simplified placement. Jejunostomy tubes are indicated in patients that are unable to tolerate intragastric or intraduodenal feeding despite having a normal distal small intestine and colonic function. Such conditions include gastric outlet obstruction, recurrent aspiration, gastroparesis and pancreatitis. A continuous rate infusion of diet is recommended when using this method. Complications include wound infection and dehiscence, tube migration/removal and subsequent peritonitis or subcutaneous cellulitis development.

DIET SELECTION

The type of formula to feed the patient will depend on the route of feeding, the functional status of the gastrointestinal tract, and the patient's nutrient requirements. Other factors, such as cost, availability, and ease of use may also be important. Liquid enteral formulations or veterinary therapeutic diets designed for enteral tubes are necessary when using naso-esophageal or jejunostomy feeding tubes. Most commercially available liquid diets have a caloric density of approximately 1 kcal/mL. Most human liquid enteral formulas contain less than 20% protein calories, precluding their use for the long-term (longer than 3 weeks) feeding of cats. Lower protein formulas should be supplemented with protein modules adding approximately 15 to 30 g casein or whey powder per 8 fl oz. can. Almost all human liquid enteral formulas lack taurine, an essential amino acid in cats, necessitating its supplementation (250 mg taurine per 8 fl oz. can) in this species.

Commercial blenderized pet food diets should be used for feeding when using pharyngostomy, esophagostomy, or gastrostomy tubes. Food should be withheld for 24 hours to allow gastric motility to return, and the formation of a fibrin seal after placing a gastrostomy tube. Diet can be administered as bolus feedings or continuous infusion when feeding via gastrostomy tube. If continuous feeding is employed, it should be interrupted every 8 hours to determine the residual volume by applying suction to the feeding tube. If the residual volume is more than twice the volume infused in one hour, feeding should be discontinued for 2 hours, and the rate of infusion decreased by 25% to prevent vomiting. Jejunal feeding can be started within 6 hours of tube placement if peristalsis is present. A constant rate infusion is preferred to administer jejunostomy feedings to avoid abdominal cramping and diarrhea associated with bolus feeding via this route.

Begin feeding approximately 25% of the patient's calculated energy requirements. Gradually increase the amount fed until the patient's energy requirements are met, usually within 3 to 5 days. The food should be warmed to room temperature and fed slowly through the tube to prevent vomiting. Flushing of the tube with 15 to 20 mL of lukewarm water will help prevent clogging. Before each feeding, aspirate the tube with an empty syringe to check for residual food in the stomach from the previous feeding. If more than half of the last feeding is removed from the stomach, skip the feeding and recheck residual volume at the next feeding.

MONITORING

Monitoring of body weight, temperature, hydration status, pulse rate, respiration rate, and attitude is recommended at least daily. Monitoring of blood parameters such as glucose, electrolytes, serum blood urea nitrogen, albumin and packed cell volume may also be useful. If sustained weight loss is noticed despite administration of full calculated RER, the caloric intake may need to be increased.

Unless otherwise contraindicated, oral food may be offered while the feeding tube is in place. Care should be taken to keep a record of food provided through the tube as well as voluntary intake. Do not consider removing the feeding tube until voluntary intake reaches at least 75% of RER. This author advises leaving the feeding tube in place for a week or two after returning to 100% of RER to ensure the cat continues to eat well.

PARENTERAL NUTRITION

Parenteral Nutrition (PN) is the intravenous administration of energy and protein. Indications for PN include an intolerance of oral feeding, risk of aspiration, severe malabsorption and pancreatitis. The three major components of TPN are lipid, amino acids, and dextrose.

Parital parenteral nutrition (PPN) only supplies part of the nutritional requirements of the patient, but it is a viable short-term alternative to PN. PPN can be administered through a peripheral vein and is sometimes called peripheral parenteral nutrition. Generally, PPN is used for short-term nutritional support in nondebilitated patients (ie, those without obvious signs of malnutrition). Other indications for PPN include patients in which central catheter placement is contraindicated and to supplement enteral feeding when it is insufficient to meet the full caloric requirements of the patient.

A detailed description regarding parenteral nutrition is beyond the scope of this article; however multiple resources exist in the veterinary literature for those who are interested. PN and PPN formulations can be obtained from a number of sources, and worksheets for custom formulations are available. Alternatively a custom formulation can be obtained from many nutrition services at veterinary referral institutions. Moreover, there are also a number of pharmacies that will compound PN if a formulation is provided, eliminating the need to prepare them in your practice.

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FELINE OBESITY – TOP TIPS FOR SUCCESS WITH WEIGHT MANAGEMENT PROGRAMS

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Obesity, defined as an excessive amount of body fat, is one of the most common medical diseases in cats, and has a number of health and welfare implications, most notably in that it decreases both quality and quantity of life. In this respect, obesity may predispose to a number of medical conditions. Many of these have serious consequences for health and welfare. The major diseases associations reported include diabetes mellitus, lameness, urinary tract disorders, dermatologic diseases, respiratory diseases, and neoplasia. Active management of pet obesity therefore has a number of potential benefits for the health and welfare. This article discusses the treatment of feline obesity and provides useful tips to maximizing success.

INITIATING DISCUSSIONS WITH THE OWNER ABOUT OBESITY

Discussion about obesity should be initiated in a way that does not imply blame or reflect on the owner's own weight. Excess weight of cats is often the result of inappropriate owner behavior. Therefore, it may be difficult to convince owners that their cat has a health problem that needs to be addressed.

ESTABLISHING OWNER UNDERSTANDING AND COMMITMENT

The success of any intervention is dependent upon the commitment and motivation of the pet owner. It is therefore essential for the veterinarian to verify that these are in place before any weight reduction program is implemented. The initial level of owner motivation depends on the way in which the case initially presents to the veterinarian, which includes:

- **Owner driven**. The owner seeks advice about a possible weight problem.
- **Associated disease**. The owner presents the dog or cat for condition which is potentially related to obesity.
- **Unrelated visit**. The obesity problem is an independent observation, made by the veterinarian, eg, during an annual vaccination or routine health check.

The first scenario is the easiest in terms of client management but, unfortunately, is the one which is least likely to occur. By definition, these owners are already motivated and have accepted the need for intervention. The next easiest are those pets that have an associated medical problem, and weight loss is required as a component of their overall management. In these cases, it is important to explain how excess weight may have caused or contributed to the disease in question, and thus how it is an essential part of maximizing response. Communicating that the obesity is a medical, rather than cosmetic, problem increases owner motivation and compliance. The most difficult scenario occurs where obesity is diagnosed in an apparently healthy cat. Initiating discussion in these cases can be problematic because the reaction of the owner is less predictable. Some may simply not believe that there is a problem. The focus of discussion should be on the health of the pet including any existing morbidity and the potential for future health problems as a result of continuing obesity. Sometimes owners are not convinced by an argument about problems in the future, if current health appears (to them) to be normal. In these cases, it may be sensible to focus on ways in which the obesity might be affecting current quality of life, eg, fitness, physical activity, and grooming.

In some situations, the owner may not be convinced straight away. Owner motivation and compliance are essential prerequisites for successful weight management, and without them there may be little point in embarking upon a weight reduction program at that time.

SETTING OWNER EXPECTATIONS

Successful weight loss depends mainly on owner commitment, so it is vital to ensure that the owner has realistic expectations from the outset. The timescale of treatment, the level and rate of weight loss, cost of therapy, behavioral changes in the pet, the time commitment for lifestyle changes (eg, exercise), and any other potential pitfalls should be discussed. The aim should be to make sure that the owner is fully informed of all eventualities, avoiding unexpected surprises.

CALCULATING TARGET BODY WEIGHT

An estimate of ideal weight can be made from the current body weight and condition. Assuming that each point (on a 9-point body condition score) or half point (on a 5-point condition score) correlates with ~10% increase in body weight, a simple mathematical equation can then be used to estimate ideal weight:

Current weight = 8.0 kg
↓
Current condition score = 9/9 (~ 40% overweight)
↓
Ideal weight = 8.0 kg – (8.0*40/100) = 4.8 kg

ACHIEVING OPTIMAL RATES OF WEIGHT LOSS

The recommended rate of weight loss remains a controversial issue in veterinary medicine. Studies have shown that excessively rapid weight loss can have deleterious consequences. Work in colony cats showed that marked energy restriction (to 45% of maintenance energy requirement at target weight) leads to more rapid weight loss (~1.3% per week) in cats than moderate energy restriction (60% of maintenance energy requirements leading to ~1% body weight loss per week); however, the consequence is that lean tissue loss is greater (18% compared with 8%). Based upon this work, weight reduction strategies should aim to produce weight loss of approximately ~1% body weight loss per week. Nonetheless, the exact rate should be tailored to each individual case, and slower rates of weight loss are acceptable if tolerated by client and veterinarian.

WEIGHT MANAGEMENT STRATEGIES

The main strategy for weight loss in cats is a combination of dietary caloric restriction and lifestyle changes. This involves either a reduction in energy intake (eg, dietary management) or an increase in energy expenditure (eg, increasing physical activity through lifestyle changes). In reality, while the latter may assist in weight loss, it is rarely successful if used as the sole component. For any intervention to be successful, close monitoring is vital. The approach chosen for any one case may vary and, as a result, the following guidelines are deliberately general.

Dietary Management

It is inadvisable to use a standard maintenance ration for weight loss because most nutrients are balanced to the energy content of the ration and, when this is restricted, there may be the potential for states of malnutrition to develop. Instead, the use of a diet that has been formulated for weight loss is recommended. A variety of diets are available for use; the main method of weight loss is caloric energy restriction. Although formulations may vary, most have some or all of the following characteristics:

- Reduced energy density, usually through a reduction in fat content.
- Increased micronutrient (vitamin and mineral) content relative to energy content.
- Increased protein content relative to energy content.
- Supplemented with L-carnitine.
- Fiber supplementation.

In order for weight loss to occur, the number of calories fed must be restricted. ***It is essential to base the calculations on the target body weight and not the current weight*** (see below). The exact allocation will vary depending upon the characteristics of the patient, the chosen diet, and other factors (amount of and ability to exercise, etc.). Veterinarians should be familiar with the guidelines for the diet they wish to use, and seek advice if necessary. The initial allocation is only a starting point; during the weight loss program, the level of allocation usually needs to be modified, usually by decreasing the amount given. Weighing the daily food ration out on electronic weight scales is strongly recommended, since other methods of determining the amount to feed (eg, measuring cups) can be unreliable.

It is essential to ensure that no additional food is given by the owner (or scavenged). However, healthy treats may be allowed as this enables the owner to maintain their bond with the cat. This should, of course, be factored into the overall calorie provision and not on top of it. Owners should also be made aware that liquids are part of the diet and so the caloric value of drinks must be included as part of the overall plan.

Lifestyle Alterations

Alterations in lifestyle include changes designed to increase energy expenditure (eg, increasing level of physical activity, introducing regular play sessions), improve quality of life (eg, regular play activity in cats), and changes in feeding pattern (e.g. accurate measuring [and recording] of daily food intake, avoiding uncontrolled feeding of extras). These strategies will be covered in more detail in the author's lecture on lifestyle alterations.

Monitoring

It is essential to follow the progress of patients frequently during any weight management program, particularly during the initial period, since this is when owners need the most support and when problems are most likely to be encountered. This provides an opportunity to verify compliance, deal with any issues or concerns (side effects of pharmaceuticals, begging behavior), and to provide feedback, encouragement, and support.

The frequency of return visits during treatment is critical: a check every 2 to 4 weeks is ideal; if check-ups occur less frequently then every 4 weeks, compliance with the program will slip. It may also lead to a delay before a change is made, meaning that weight loss does not continue at an optimal rate. Each return visit should include weighing and a physical examination as well as a general discussion about behavior (exercise/treats, etc.) and progress. Body weight is the principal outcome measure of interest and should be used to decide whether changes to the plan are required (reduction in amount of food fed, increase in dose of medication). In order to minimize variability among measurement, the same electronic scale should be used and regularly validated.

In addition to the results for the bodyweight measurement, the body condition score chart can be used as a visual aid for leading discussion and providing owners with positive feedback. However, given that body condition is likely to change gradually, it is not essential to repeat the body condition score at every visit. Morphometric measurements (eg, thoracic circumference, abdominal circumference) are an additional means of monitoring outcome, and can be used to relay success in terms that the owner will understand (eg, similar to a decrease in the size of the waist in people). Periodic photographs provide and excellent visual demonstration of success, but should be taken in a standardized manner to enable comparison between time points.

All measurements and comments should be recorded and used to provide positive feedback, wherever possible, for the owner. As mentioned above, it is vital for veterinarians to encourage owners to record the food intake of their dog each day, and to review this information at each visit. Incentives such as "slimmer of the month" awards or achievement certificates are used successfully as motivational tools in human weight loss programs, and are therefore worth considering for pets. Owner motivation is the key to a successful outcome. Even if these are not used, it is still important to set targets so that owners have something to aim for and a sense of achievement when they reach their goal. Follow-up by phone, for example, by a nurse or animal technician responsible for overseeing the program, is an excellent means of checking on progress, enhancing compliance, and addressing any problems as early as possible. The involvement of other members of the veterinary team is a good way to boost success and make owners appreciate the commitment of the practice.

Successful Weight Maintenance

Although the main medical benefit of a weight reduction program is a long-term reduction in adipose tissue mass, of greater importance is the permanent switch to a healthy lifestyle. As such, success depends not only on reaching the target, but in avoiding any rebound. While pharmaceuticals can be used in effecting weight loss, they are not currently recommended for maintenance. Therefore, maintenance relies on the other strategies discussed above, namely dietary modification and lifestyle alteration.

In short, a permanent change in the attitude and behavior of the owner is required to ensure that any weight loss is maintained long term.

Once target weight has been achieved, regular checkups should continue, as well as the support and encouragement for the owner. Cats should be fed at maintenance, rather than for weight loss. One method of transition is to increase the food intake by 10% every 2 weeks until no further weight loss is achieved. This will enable the veterinarian to set the daily caloric requirement to prevent weight gain. Visits every 2 to 4 weeks should continue until the veterinarian is satisfied that weight is being maintained. Thereafter, the interval between weigh-ins can gradually be extended but should not be less frequent than once every 3 to 6 months.

The choice of diet for the maintenance phase is less critical than that used for weight loss. There should be no need to feed a diet specifically formulated for weight loss on a long-term basis. Diets are available for use in the post-weight loss phase, and contain many desirable characteristics, including reduced energy content and increase fiber level (to promote satiety).

References are available upon request from the author.

EXERCISE PROGRAMS FOR FELINE OBESITY – HOW TO MAKE THAT FAT CAT FIT

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Obesity is defined as an excessive amount of body fat, and is one of the most common medical diseases in cats. Excess weight has a number of health and welfare implications, most notably in that it decreases both quality and quantity of life. Treatment of feline obesity therefore has a number of potential benefits for health and welfare. Weight management regimes in cats typically involve dietary caloric restriction and increased energy expenditure.

PROMOTING A HEALTHY LIFESTYLE

During a weight loss regime, it is important to instigate a healthy lifestyle, which is as critical to long-term prevention of weight gain as it is to weight loss. Alterations in lifestyle include changes designed to increase energy expenditure (eg, increasing level of physical activity, introducing regular play sessions), improve quality of life (eg, regular play activity in cats), and changes in feeding pattern (eg, accurate measuring [and recording] of daily food intake, avoiding uncontrolled feeding of extras).

INCREASING ENERGY EXPENDITURE

The aim should be to increase the level of activity in gradual steps and to make it a regular feature of the cat's life. The benefits of increasing physical activity go beyond the fact that it burns calories. In humans, when used in combination with dietary therapy, it promotes fat loss and may assist in lean tissue preservation. It may also enhance the pet/owner bond, provides mental stimulation, and generally improves welfare and quality of life. Finally, there is also some evidence that exercise may help prevent the rapid regain in weight that can occur after a period of successful weight loss.

Methods of Increasing Physical Activity

The exact exercise program must be tailored to the individual, and take account of any concurrent medical concerns. It should also take into account the existing capabilities, as well as the age, health, and other conditions of the owner. The aim should be to increase the level of activity in gradual steps and to make it a regular feature of the cat's life. The type of physical activity recommended will vary depending upon the individual.

Methods to increase physical activity in cats include:

- increasing play activity
- encouraging the cat to exercise itself
- increasing movement through the use of food treats.

When implementing regular play activity, it is best to start with two short (~2 to 3 minutes) sessions each day). This will not overburden the owners, and will allow the cat to become accustomed to the activity. Once a regular level of activity is established, and as weight loss progresses, it is possible to increase the duration and intensity of the exercise/play sessions.

During a play session, cats must be given the opportunity to catch the "prey" object. A number of toys designed specifically for cats are now available; some features of good cat toys include:

- ability to produce rapid and unpredictable movement
- emission of a high-pitched sound
- small "prey" size
- ability to supply a food reward.

Examples of good cat toys include fishing rod toys although some home-made objects can work equally well (eg, rolled up paper, tin foil). Feline play stations are another means by which cats can both exercise and fulfil their natural behaviours; these incorporate the opportunity to climb, balance, scratch, and hide. The best-designed stations are those that provide many and varied levels and climbing options (thus making full use of three-dimensional space), include dangling toys and scratch posts. Scratching is an additional means by which cats can expend energy; posts that allow the cat to stretch at full stretch are best.

Food can also be a useful motivator for physical activity. Hollow toys can be purchased or constructed that contain small amounts of kibbles. The cat must then play with the toy (thereby expending energy) to receive the reward. This solution diverts the cat, decreases its boredom when living exclusively indoors, and helps to reduce overall food consumption.

References are available upon request from the author.

THE FELINE PERSPECTIVE: NOTHING IS AS EASY AS IT LOOKS

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Carly is a 16-year-old female spayed Persian cat presented for poor regulation of diabetes mellitus. Carly had been diagnosed with diabetes 2 years previously and was well controlled. The owner performed regular serial glucose curves and noted difficulty achieving satisfactory blood glucose regulation over the past month. Increased appetite, water consumption, and urination were noted. Other problems listed for Carly included early renal disease (IRIS Score 2, non-proteinuric), controlled hypertension, and recurrent urinary tract infections.

Current treatment included 3 U UltraLente insulin SQ BID, amlodipine, potassium gluconate, ranitidine, SQ lactated Ringer's solution (75 cc) every other day, and a mixture of premium maintenance dry foods and Hill's Feline Prescription Diet® w/d dry fed free choice and Whiska's Sheba® canned (fed in small amounts four times daily). Physical examination revealed mild dental disease, bilaterally small and irregular kidneys, a large bladder, body conditions score of 3 (on a 5-point scale).

What are possible causes for Carly's change in regulation? What is your diagnostic plan?

A complete blood count, blood chemistry, electrolytes, T4, fructosamine, urinalysis, urine culture, and abdominal radiographs and ultrasound were performed. Radiographs, laboratory results, and serial glucose curves provided by the owner upon presentation were also available.

Evaluation of the data confirmed decreased glucose control based on the serial glucose curve, marked glucosuria, and increased fructosamine compared to previous levels (values from 323–359 μmol/L). Radiographs and ultrasound supported physical findings of small irregular kidneys compatible with chronic renal disease. Mineralization of the left kidney as noted. Carly had previous episode of urinary tract infections, but was negative on urine culture and had no other evidence of urinary tract infection at this visit. Owner insulin administration technique and insulin quality was considered appropriate. While chronic oral disease and infection can contribute to insulin resistance and poor diabetic regulation, the level of dental disease noted in Carly was considered mild and unlikely related to her decompensation. Low-grade pancreatitis was also considered but excluded based on normal abdominal ultrasound and lack of clinical signs. Thus, a specific cause for the change in glucose regulation was not immediately apparent.

The owner was advised of different options for improving diabetic regulation. Discussion points included increasing insulin dose or frequency, altering insulin type to longer-acting forms (ie, glargine), or use of low-carbohydrate diets. Because diabetic regulation was the most significant medical problem, and Carly had not been provided dietary support for her renal disease, the owner chose to try a low-carbohydrate food designed for management of feline diabetes. Low-carbohydrate foods have slightly higher protein than high-fiber formulations designed for diabetic regulation. For that reason, manufacturers suggest caution when feeding low-carbohydrate foods to cats with renal or liver disease. Because Carly's renal disease was mild, and the total dietary protein intake was only slightly greater than her current diet, the owner was anxious to try low-carbohydrate feeding.

Carly was provided Hill's Prescription Diet® m/d dry and canned food. A 4-day transition to the new food was recommended. The owner reported Carly appeared to like the new diet, her appetite was better controlled, and her polydipsia was improved.

Week 4

Four weeks following introduction of the new low-carbohydrate food, Carly had lower levels of urine glucose and much improved blood glucose regulation based on the results of random blood glucose checks and a serial glucose curve. However, Carly's owner was concerned that Carly appeared somewhat lethargic and her appetite had recently declined.

Carly was represented for evaluation. The physical exam was unchanged from the previous visit, except for the slight lethargy noted by the owner. Laboratory evaluation included a CBC, chemistry, electrolytes, fructosamine, urinalysis and culture.

The serial glucose curve, fructosamine, and urinalysis demonstrate markedly improved glucose regulation. Ideally, this therapeutic plan should be continued. Unfortunately, the chemistry panel revealed a significant increase in creatinine and BUN (2.9 mg/dL and 60 mg/dL, respectively). Despite the minor increase in dietary protein, the new diet appeared to contribute to increased azotemia when coupled with the cat's ongoing renal disease. The owner agreed to attempt diabetic regulation using a renal therapeutic food (Hill's Prescription Diet® Feline k/d). Increased frequency of subcutaneous fluids improved Carly's attitude and she readily consumed the new food.

Week 6

Carly returned for reevaluation 2 weeks later. Diabetic regulation had again deteriorated based on the home serial glucose curve and elevated fructosamine levels (433 μmol/L). Creatinine levels had returned to normal and BUN were only slightly elevated (1.8 mg/dL and 38 mg/dL, respectively). The owner indicated Carly appeared to feel better on the new food despite her poor glucose control.

Because the diabetic regulation responded well to low-carbohydrate feeding, acarbose was started to inhibit intestinal glucose absorption and the insulin dose was adjusted to 3.5 units BID. Carly's owner indicated improved in glucose control, attitude and appetite using the new diet, insulin, and acarbose therapy.

Week 8

Two weeks later, Carly began to have soft to watery diarrhea. The large volume, increased frequency, and urgency suggested a mixed small and large bowel disorder. These signs were considered side effects of the acarbose as undigested carbohydrates can be fermented and contribute to bacterial overgrowth. A fecal flotation, fecal culture, fecal enterotoxin assay, and blood for serum pancreatic lipase immunoreactivity (PLI), trypsin-like immunoreactivity (TLI), B12 and folate were submitted.

Laboratory results were consistent with bacterial overgrowth based on elevated TLI and low B12 levels. Acarbose therapy was discontinued and Carly was treated with metronidazole and vitamin B12 injections. Her stool remained intermittently soft. In order to maintain glucose regulation and improve stool quality, a 60:40 blend of the renal therapeutic food and fiber-fortified diet (Hill's Prescritpion Diet® Feline k/d and w/d) was chosen. Carly's stools returned to normal and her glucose regulation and renal disease remained adequately controlled for the following 2 years.

RAW FOOD DIETS: WHAT A NUTRITIONIST THINKS YOU SHOULD KNOW

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Raw foods are the evolutionary diet of all creatures. Dogs and cats in particular evolved eating raw meat as the primary (dogs) or sole source (cats) of food. In the 20th century, commercially manufactured foods became common for people as well as pets. In the past 50 years, pet food manufacturing has grown to a 10 billion dollar industry and provides food for over 90% of US pets. Yet, a growing number of pet owners have turned to raw food feeding. Surveys suggest approximately 8% of dog owners and 4% of cat owners provide raw food as the main component of the diet. Those that support raw food diets are highly passionate about the benefits, claiming improved pet health, reversal of chronic disease, elimination of allergies, cancer prevention, and a host of other benefits. Despite these claims, wholesale acceptance of raw food feeding is limited.

SOURCE OF RAW FOOD DIETS

The majority of raw diets are home prepared from recipes garnered from books, self-design, or the Internet. There are also several commercially available raw foods that range from complete foods (sold frozen) to mixes to be used with freshly purchased meats.

RATIONALE FOR FEEDING RAW FOODS

The rationale for feeding raw foods is multifactorial but basically divides along lines of health and/or safety. In addition, some owners simply like to have a significant input into their pets health and can do so by designing and preparing the diet. On the "health side," an overlying premise is that dogs' and cats' ancestral food was raw meat and this represents the optimal nutritional profile for health and longevity. In addition, the ability to select the quality of the ingredients (ie, organic, non-GMO, or prime cuts) alleviates their concern over the safety of commercially manufactured foods. From this safety perspective, raw feeding helps to avoid preservatives, additive, colorants, toxins, grains, and a number of other components that may be in manufactured food.

The ability to chose ingredients, select quality, and avoid certain chemicals can be a benefit to home prepared foods; however, the major health reason for not cooking these foods is the perceived benefits of active enzymes in uncooked tissue, along with increased vitamins and minerals. Active enzymes are thought to restore and maintain health, alleviate stress on the pancreas and provide the benefit of unique phytochemicals, antioxidants, and unprocessed amino acids. The enzymes in raw food are thought to improve digestibility and availability of nutrients in the food.

Testimonials claim healthy teeth and clean breath without brushing, luxurious skin and coat, optimum immune system, improved stool, and better weight control. With such claims, why are so many veterinary nutritionists not at the forefront of the raw food movement? Ironically, it is the same rationale offered by those that favor of raw food feeding: concern over nutritional adequacy and safety. In addition, peer-reviewed studies supporting the claimed benefits of raw foods are lacking; thus the weight of benefit to risk seems somewhat lacking. The goal here is to describe some of the evidence regarding raw foods from a nutritional perspective. Hopefully this will allow veterinarians to consider raw food support or caution from a position of science.

DIGESTIBILITY

Heat processing both improves and diminishes the digestibility of foods. Typically, heat processing improves carbohydrate digestibility and that of some amino acids (lysine in wheat). Alternatively, high heat processing reduces the digestibility and bioavailability of other amino acids (lysine in milk, methionine, arginine, taurine availability). Maillard reaction products, where free sugars combine with free nitrogen groups of certain amino acids, are known to reduce digestibility of proteins. Thermal processing can cause structural changes in proteins and amino acids. Heterocyclic amines develop under conditions of high thermal processing. Some epidemiologic studies in people suggest increased risk of cancer with exposure to these altered amines. When feeding cats an identical diet, either heat processed or frozen, this author noted total protein digestibility declined by approximately 5% to 7% in the cooked food compared with the raw diets. Carbohydrate and fat digestibility was improved with thermal processing. Certain antioxidants are more available following heat processing (cis-lycopene). Therefore, a consistent benefit of raw food feeding on digestibility is not seen, however high heat often limits protein availability in certain foods. Fahey et al found improved digestibility in fresh beef compared to a rendered beef diet.

NUTRITIVE FACTORS

Raw and frozen foods do retain a portion of enzymatic activity even up to 6 months. Health benefits to dogs and cats have been described in dogs with exocrine pancreatic insufficiency receiving frozen pancreas as a mode of treatment (Westermark, 2001). This is a popular form of therapy in Europe and supports the contention that sufficient enzyme activity exists in frozen products to have biologic activity. Conversely, raw ingredients can have antinutritive factors (eg, soybean trypsin inhibitors) that negatively influence food utilization and have been implicated in pancreatic cancer in murine models.

NUTRITIONAL ADEQUACY

Standard testing protocols used to define nutritional adequacy have been called into question by some. AAFCO feeding protocols are designed to evaluate performance of foods for a 6-month period of time and could overlook inadequacies that take a longer period to develop. The minimum nutrient requirements and recommended allowances established by NRC provide reasonable guidelines for those who would formulate and prepare homemade foods. The difficulty in preparing and feeding raw or home-prepared foods concerns three key issues: a) what is the skill and training of those formulating the diet; b) are the ingredients of good quality, well defined, and consistent in nutritional profile; c) are the diets being consistently made to specifications? These are the same factors that are assessed daily by commercial pet food manufacturers.

Published reports are not comforting when evaluating the adequacy of available diets for home formulation. When three diets were prepared by owners and evaluated for adequacy, all were either excessive or deficient in key nutrients. In a study evaluating the nutritional adequacy of published diets, 86% of the diets were not complete. Factors contributing to the inadequacy were poor detail of ingredients, lack of adequate supplementation, and lack of ingredient knowledge. Finally, another factor contributing to feeding suboptimal foods is lack of owner consistency in preparing the diet as described. In this author's experience, owners who are not fully committed to home-preparing food tend to end up with a diet drift (diet Darwinism) such that a balance food becomes unbalanced over time. Despite the small percentage of home-cooked feeders, the number of animals reported to have adverse effects from home-prepared foods is proportionally high. Metabolic bone disease is frequently noted and is commonly seen in our nutrition practice among large cats held by private owners. In addition, taurine deficiency is known to occur in raw meat diets. Owners and veterinarians assume that all meats are high in taurine. While generally true, the butchering and grinding process allows taurine to be lost in the blood. Several cases of taurine deficiency have been diagnosed in cats fed whole meat diets.

FOOD SAFETY

Certainly concerns over the safety of commercial foods have heightened following the widespread Menu Foods recall. Owners who are uncertain how to determine food safety and quality are looking toward alternative feeding practices. Natural, organic, and human grade foods have consumer appeal compared with byproducts and meat meals from the slaughter industry. Books and Internet blogs claiming euthanized dogs and cats are in pet foods, evidence of pentobarbital contamination in some foods, and a general distrust of big business have fueled fears that commercial foods are unwholesome. Certainly significant food toxicities have occurred in the past, as well as examples of nutritional inadequacy in commercial diets. In general, these incidents have resulted from human error and lack of appropriate oversight. New regulations, tighter scrutiny, and an emphasis on quality control are expected to improve deficiencies. Nevertheless, recent recalls of *Salmonella*-contaminated foods have been linked to human illness.

The safety of raw foods has also been brought into question. There is clear evidence that bacterial contamination with pathogenic bacteria is common and poses potential harm both pets and people. High proportions of commercial and home-prepared raw foods have been identified with bacterial and parasitic pathogens (Strohmeyer, 2006). Seven of 16 dogs fed *Salmonella*-infected meat shed the bacteria in their feces although none were clinically affected (Finley et al, 2007). Over 60% of raw diets fed to greyhounds were contaminated (Chengappa, 1992). In another study 100% of 25 commercial raw diets had significant bacterial contamination (Weese, 2005) Survey of raw foods (commercial and home-prepared) found *Salmonella, E. coli, Campylobacter, Clostridium, Staphylococcus, Toxoplasma,* and *Cryptosporidium* organisms. While most animals are unaffected by the levels of bacterial contamination presented, there are published reports death related to septicemic salmonellosis in two cats fed a home-prepared raw-meat diet (Stiver, 2003).

INJURY FROM BONES

Bones from any source have potential to cause safety concerns in dogs and cats. Bone foreign bodies, constipation, gastroenteritis, esophageal and intestinal obstruction, organ perforation and septic peritonitis have all be report to occur with bone feeding. Proponents of raw food feeding note bones are less likely to splinter if cooked. Unfortunately, most internists have had the challenge of removing a bone from the esophagus dog or deal with complications of septic peritonitis secondary to perforation. Fortunately, the occurrence is indeed relatively uncommon.

HEALTH BENEFITS

To date, published data supporting a health benefit of raw foods are largely testimonial. A study designed to asses wound healing and raw food feeding was initiated but never completed. So while concerns of commercial foods abound, it is hard to assess raw food health benefits beyond testimonials.

ENVIRONMENTAL/RESOURCE CONSIDERATIONS

Feeding human-grade ingredients to pets has ethical and environmental impact. A majority of today's poultry and livestock are raised in confined feeding/farming operations. Only about one third of an animal carcass is designated for human use (human-grade food). The remainder is available for pet foods, fertilizer, and rendered products. Pet food manufacturing does utilize the less desirable portions of our animal resources (spleen, liver, gullet, intestines, etc.). Utilization of these "byproducts" increases stewardship of our animal resources and the environment they live in.

PRACTICAL CONSIDERATIONS

When weighing the risk and benefit of raw food feeding, more data is clearly needed. It is possible to feed raw foods and maintain vitality in dogs and cats, but a clear benefit is not evident in the literature. Choosing fresh, high-quality ingredients and using scrupulous safe food-handling techniques is imperative. The FDA provides guidelines on handling raw foods at: http://www.fda.gov/cvm/foodbornetips.htm.

References are available from the author upon request.

FDA Guidelines on Raw Food Diets for Pets

The FDA does not advocate a raw meat, poultry, or seafood diet for pets, but is stepping up its efforts to minimize the risk such foods pose to animal and human health because we understand that some people prefer to feed these types of diets to their pets. For the protection of both you and your pet, the FDA recommends you follow these instructions when handling or using raw meat, poultry, or seafood, for use in a pet's diet:

Keep raw meat and poultry products frozen until ready to use.
Thaw in refrigerator or microwave.
Keep raw food diets separate from other foods. Wash working surfaces, utensils (including cutting boards, preparation and feeding bowls), hands, and any other items that touch or contact raw meat, poultry or seafood with hot soapy water.
Cover and refrigerate leftovers immediately or discard safely.
In addition:

For added protection, kitchen sanitizers should be used on cutting boards and counter tops periodically. A sanitizing solution can be made by mixing one teaspoon of chlorine bleach to one quart of water.
If you use plastic or other non-porous cutting boards, run them through the dishwasher after each use.
For additional information about safe food handling, please see http://www.cfsan.fda.gov/~dms/qa-topfd.html.

FOOD AND IMMUNITY: COULD YOU BE DOING MORE?

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During injury and illness decreased food intake, stress, and medications can alter immune function. The immune response can be critical to providing protection against infection and initiating tissue repair, or may exacerbate the disease process with ongoing inflammation and cellular destruction. Before initiating nutritional therapy, it is important to determine the desired response. Key nutrients can serve to either enhance or suppress the immune response. As such, nutritional modification of the immune response can be an important contributor to the overall health of an animal.

One of the most common aspects of systemic disease is illness-induced anorexia. When poor food intake is combined with protein catabolism, generation of reactive oxidation species, and release of inflammatory mediators it contributes to impaired immune response, diminished tissue barrier function (ie, gut-associated lymphoid tissue), and ongoing metabolic complications. It is important to recognize the benefit of some of these nutrients and prioritize their value in immunomodulation.

GENERAL MALNUTRITION

Malnutrition can describe inadequacy in one or several nutrients. Deficiency of protein and energy (calories) are commonly observed in the small animal patients with prolonged anorexia. Protein-calorie malnutrition (PCM) may occur alone or in combination with other vitamin and mineral deficiencies. PCM has broad effect on the immune system. Both humoral and cell-mediated immunity is suppressed. There is impaired response of lymphocytes to mitogens, neutrophil dysfunction, immunoglobulin and complement components are depressed, and there is suppression of acute-phase reactants. Anatomic barrier to infection and damage are impaired following atrophy of the skin and GI mucosa. The risk of local and/or systemic infection increases with ongoing PCM. The most effective means of maintaining adequate immunity is through some form of nutritional support. To correct and prevent deterioration of immunity, early feeding should be initiated. Most studies in people and animal models suggest mortality and morbidity are reduced when feeding is initiated within 48 hours of hospitalization. Many times nutritional support of small animals is not considered until a prolonged period of anorexia is evident (5 or more days). Consideration for early nutritional support may be the easiest and most effective method of nutritional support of immune function.

PROTEIN AND AMINO ACIDS

In disease and hypermetabolism, the requirement for protein may increase. A similar finding of immune suppression occurs in protein malnutrition just as in combined PCM. Support for lean tissue mass and protein balance is critical for recovery from trauma and disease and for normal immune function. In studies of burn patients, survival increases with increased protein provision. Major pet food manufacturers produce critical care/recovery formulas that are high in proteins and supplemented with key amino acids to help protect body protein stores and enhance immune function and tissue repair. These formulas represent and easy means to provide nutritional support via enhanced oral intake or through feeding tubes. Most enteral formulas provide between 4 and 6 g protein/100 kcal for dogs and 6 to 8 g protein/100 kcal for cats. These levels of protein intake are considered optimal for animals with normal protein tolerance under nutritional support. In addition to maintaining general protein nutrition, single amino acids have specific immune-enhancing properties.

ARGININE

Arginine is an essential amino acid in cats and growing dogs. It is a critical nutrient in wound healing and immune function. Arginine supplementation is known to improve cellular immunity through a variety of mechanisms. Increased T-lymphocytes blastogenesis, nitric oxide production, interleukin-2 (IL-2) production, stimulation of natural killer (NK) cells, suppression of tumor angiogenesis, and tumor killing have all been attributed to arginine. Arginine has been shown to enhance nitrogen balance in people and animal models of disease and trauma. Dietary supplementation in animal models has supported a benefit of arginine at 2% of the diet.

GLUTAMINE

Glutamine is a nonessential amino acid that is considered conditionally essential during disease and metabolic stress. Glutamine is considered a primary fuel source for the enterocyte and helps protect against gut atrophy and bacterial translocation across the bowel. Plasma glutamine levels have been shown to drop by over 50% during injury or illness. Glutamine deficiency can impair lymphocyte and neutrophil function. Glutamine enrichment of diets increases T-lymphocyte proliferation, cytokine production and significantly decreases sepsis, pneumonia, and bacteremia. Glutamine is also a nitrogen donor for the synthesis of purines and pyrimidines, proteins synthesis and glutamate which is important in the generation of glutathione (GSH). An established dose of glutamine in dogs and cats is lacking. Empirical dosing of 0.5 mg/kg PO has been suggested. Glutamine has been used to support gut barrier function in parvo enteritis and in a model of feline chemotherapy enteritis. Neither report showed a significant benefit over providing a balanced whole diet. Negligible side effects have been reported with use.

FATTY ACIDS

Omega-3 fatty acids have long been known to alter immune function through suppression of the inflammatory response and inhibition of cytokine output.

The omega-3 (n-3 series) fatty acids compete for the same desaturase and elongase pathways as omega-6 fatty acids. The change in eicosanoid, leukotriene, and lipoxin end products to less inflammatory constituents is responsible for the benefit. Omega-3 fatty acids require 6 to 16 weeks of intake to maximize blood levels. The rate of accumulation is dependent on dose. Thus, an acute benefit to n-3 fatty acids should not be expected. Fish oils are the recommended source of n-3 fatty acids due to high concentrations of EPA and DHA. Flax seed oil is not readily converted to EPA by dogs and cats. Recommended dose for general suppression of the inflammatory response is 40 mg EPA/kg BW in dogs and cats. This level roughly translates into a 1 gram capsule of standard fish oil/10 pounds.

MINERALS

Iron, copper, zinc, and selenium are mineral sources that have a distinct benefit on immune function. Iron is necessary for optimum neutrophil and lymphocyte function, and is often sequestered within the body during disease as free iron is necessary for bacterial growth. A deficiency of copper have been associated with increased rates of infection, depressed reticuloendothelial system, suppressed microbicidal activity of granulocytes, impaired antibody response and is a component of the antioxidant enzyme superoxide dismutase (SOD). Thus, maintenance of normal copper intake is required to maintain normal immune function. Zinc deficiency is associated with increased infections, abnormal cell-mediated immunity, depressed thymic hormones, and altered complement and phagocytic function. It too is a component of the antioxidant network (as a component of SOD) and scavenger of reactive oxygen species.

Selenium has an important role as an antioxidant as a component of glutathione peroxidase enzyme. Studies demonstrating immune support in dogs and cats have typically included vitamin E in combination. Responses to each nutrient appeared to be independent of the nutrition of the other. Deficiencies of vitamin E and selenium conversely caused suppression of the immune response system, particularly, cell-mediated mechanisms. Specific supplementation is not normally needed beyond provision of a complete and balanced diet for enteral feeding. During parenteral nutrition, use of trace mineral supplements is recommended.

ANTIOXIDANTS

A variety of antioxidants are available. Most studied in dogs and cats is vitamin E. Vitamin E and selenium have both been shown to have immunostimulatory effects in a variety of species when administered in quantities in excess of established dietary requirements. Supplementation has been shown to enhance antibody response to vaccination, enhance neutrophil phagocytosis in geriatric beagles, reduce free radical damage of DNA and tissues, and increase lymphocyte proliferation. Other antioxidants shown to have promise in dogs and cats include lutein, vitamin E, alpha-lipoic acid, rosemary, and others. While early studies demonstrate benefit, some caution must be employed is supplementing novel antioxidants as a safe dose and toxicity testing are often unavailable. Nevertheless, antioxidant protection is beneficial to immune function and should be considered either through selection of antioxidant enhanced commercial formulas or rational supplementation. Care must be taken to gather an adequate dietary history. Many therapeutic and premium foods are enhanced with antioxidants; excessive supplementation can result in side effects and should be avoided.

NUCLEOTIDES

Nucleotides are building blocks for DNA and RNA and typically generated in vivo by de novo synthesis. During illness, dietary supplementation of preformed nucleotides has demonstrated improvement in immune response and reverse immunosuppression. Early evaluation in animals receiving parenteral nutrition has suggested beneficial effects in dogs. Additional research is needed to define optimal use.

OTHER

There are numerous nutrients and dietary supplements that have a purported beneficial effect on the immune function. Online resources and veterinary texts list hundreds of possible supplements, but scientific evidence demonstrating improved clinical outcome is limited.

RECOMMENDED READING

1. Zicker SC, Wedekind KJ, Jewell DE. Antioxidants in veterinary nutrition. Vet Clin North Am Small Anim Pract. 2006 Nov;36(6):1183-98
2. Saker SE. Nutrition and Immune Function. Vet Clin North Am Small Anim Pract. 2006;36(6):1199-1224.

A CHANGE OF HEART: NUTRIENT SUPPORT IN CANINE HEART FAILURE

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Nutritional support of canine heart failure promotes two goals: therapeutic treatment designed to support cardiac function and supportive care designed to alleviate the consequence of disease. The two most common forms of canine heart disease are chronic **degenerative valvular disease**, seen more commonly in small breed dogs, and **dilated cardiomyopathy** (DCM), identified most often in large to giant breeds.

Over the past 3 decades strategies for managing heart disease has expanded from simple sodium restriction to broader cardiac and whole body support.

NUTRIENTS OF INTEREST

A number of herbal and nutritional supplements have been advocated for cardiac support,[2] but only two have a well-documented effect in reversing or stabilizing disease: taurine and L-carnitine. Fish oil has been shown to reduce arrythmias and stave off cardiac cachexia. Antioxidants, though full of potential, have yet to demonstrate significant impact in reducing morbidity and mortality in dogs or cat.

Taurine

Taurine is a sulfur amino acid required by the cat. Taurine is found in high tissue concentration in cardiac muscle where it is known to be essential for normal myocardial function by unknown mechanisms. Proposed effects are through modulation of calcium channels. It also functions as an antioxidant, in osmoregulation, in n-methylation or as an antagonist of angiotensin II.

While taurine is not an essential nutrient in the dog, a dietary source may be conditionally essential in certain breeds and when metabolic precursors are limiting in the diet. Low plasma taurine levels were identified in conjunction with DCM in American cocker spaniels and golden retrievers. Taurine supplements together with L-carnitine have demonstrated substantial improvement. However, resolution similar to feline DCM did not occur.

Other confounding dietary factors have been identified resulting in the occurrence of taurine-related DCM in dogs. Dogs treated with cystine or urate urolithiasis and healthy beagle dogs fed low-protein, high-fat diets for prolonged periods developed taurine deficiency and low carnitine levels. Diets high in soybean protein, rice bran, and certain lamb and rice pet food formulation have resulted in low plasma taurine and DCM. Low methionine in soy and lamb has been shown to limited taurine synthesis due to limited precursor molecules. This appears more significant in large and giant breeds (Newfoundlands) where taurine needs appear to be greater. Rice bran, a fermentable fiber, is thought to promote low taurine due to destruction by increased gut microbes promoted during fermentation. Second, the high fat content of bran results in higher bile salt (taurocholate) excretion into the intestine where it can be degraded and lost in the feces. Thus, taurine has proven to be an important factor in canine cardiomyopathy of large breed dogs and cocker spaniels.

Taurine Testing – Whole blood and plasma samples should be collected after an 8-hour fast. Samples should be carefully collected in a heparinized syringe or blood collection tube. Plasma levels < 40 nmol/mL or whole blood levels < 150 mmol/mL should be supplemented.

Taurine Supplementation – Large breed dogs, especially Newfoundlands, golden retrievers, Labrador retrievers, Dalmatians, English bulldogs, and Portuguese water dogs, with DCM should be tested for taurine deficiency and treated. Not all dogs show improvement. The recommended dose is 500–1000 mg of taurine orally two to three times per day for small dogs (< 25 kg), and 1–2 g of taurine two to three times daily for dogs 25 to 40 kg.

L-Carnitine

Like taurine, carnitine is found in high amounts in skeletal and cardiac muscle. Only the L-form of carnitine is naturally in the body as opposed to the d-form, which competitively inhibits L-carnitine. Carnitine act like a shuttle to help transport long chain fatty acids into the mitochondria for beta-oxidation and energy production. Other functions include antioxidant properties, detoxicant and regulation of energy flow. Carnitine is a primary of secondary metabolic disorder. Genetic factors altering synthesis, renal transport, intestinal absorption and transmembrane uptake or excessive degradation may lead to deficiency. Secondary deficiency may occur with nutritional deficiencies, long-term parenteral nutrition, vegan diets. In dogs, both genetic (boxer) and dietary deficiencies have been reported.

Carnitine Testing – Diagnosis of carnitine deficiency can be a challenge. Dogs may present with plasma carnitine deficiency, systemic deficiency or myocardial deficiency. Plasma carnitine is often submitted as the only diagnostic sample but may miss myocardial forms of the disorder. Blood samples are collected in heparinized tubes, then chilled and harvested. Muscle biopsies and myocardial biopsies may be required to confirm a diagnosis.

Carnitine Treatment – The recommended dose of carnitine is 50–100 mg/kg orally every 8 hours. The myopathic form may need higher levels to overcome the primary transport defect. Echocardiographic improvements are not normally noted for 2 months.

Fish Oils (Omega -3 Fatty Acids)

Fish oils may be useful in heart failure to both combat cardiac cachexias as well as inhibit arrhythmias. Fish oil supplementation reduces cytokine production through modulation of eicosanoids and down regulation of cytokine transcription. By prevention of slowing cachexia, fish oils may extend life span of heart failure patients. Fish oils also reduce the electrical excitability of the myocyte and increase the refractory period to reduce the potential for arrhythmia and sudden death. Fish oils are provided in several diets or may be purchased at most stores selling vitamins. The usual dose is 1 gram capsule per 10 lbs orally twice daily.

Antioxidants

A number of studies have evaluated various antioxidants and heart failure. Surprisingly the evidence for antioxidant support has been relatively small. Vitamin E, CoQ10, and others have been promoted for years with little effect. More studies are needed in cats and dogs before recommendations can be made.

Minerals

Maintenance of adequate electrolyte balance is essential for heart function. Potassium and magnesium are commonly evaluated during cardiac dysfunction. It is unclear that supplementation would provide a protective advantage. Maintaining usual serum ranges appears adequate. Sodium has long been restricted in cardiac failure. The goal is to reduce sodium retention and fluid overload in the face of RAS activation. With newer ACE inhibitors, severe sodium restriction is contraindicated. Moderate sodium levels of between 0.25 and 0.45% dry matter appear adequate for most cases of cardiac disease.

A number of nutrients strongly influence the cardiac function, while only two have clear data to demonstrate the ability to reverse heart disease.

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FOOD TOXICITIES IN COMMERCIAL FOODS WHAT YOU NEED TO KNOW

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With the recent number of pet food recalls, issues of food safety are on the forefront of veterinary medicine. Prevention of food toxicity is always the primary goal. Unfortunately, toxins and contamination do occur and knowing the steps to take can aid make a timely diagnosis in order that product recalls and public notifications limit further exposure.

Suspecting a food contamination is the first step. Understanding how pet foods are made, knowing common food toxins and clinical signs, and recognizing clusters of disease are critical to recognizing food toxicity. Once a presumptive diagnosis is made the following checklist is suggested.

CHECKLIST FOR MANAGING A SUSPECTED PET FOOD CONTAMINATION CASE

- Retain food samples for analysis
    - Store 4 large cans or 1 kg of dry food when possible
    - Freeze and/or store at room temperature in airtight bags

- Document product name, type, and manufacturing information
    - Retain all packaging
    - Identify date codes or production lot numbers
    - Retain purchase receipts

- Document product consumption history
    - Dates foods were fed
    - Consumption or palatability history
    - Onset time of clinical signs
    - detailed diet history (ie, all items fed and feeding methods)

- Contact manufacturer

- Notify the FDA Consumer Complaints Coordinator (CCC) for state
    - A list of CCC telephone numbers for each state is available at http://www.fda.gov/opacom/backgrounders/complain.html.

- Document communication with FDA, manufacturers, and clients
    - Record date, time, and contact person
    - Maintain case ID for each patient contact

- Submit samples to diagnostic lab, CCC, or manufacturer for analysis

- Submit all deceased animals for necropsy and sample collection
    - Retain tissue samples in formalin and frozen (500–1000 grams)
    - Consult with diagnostic laboratory for required tissue quantity,
    - Preparation, storage and submission

- Maintain detailed medical records of affected animals
    - Clearly document clinical course, diagnostics, treatment and outcome
    - Retain serum and tissue samples when possible for further testing

- Notify client-consumers of potential exposure or product recalls

- Examine all pets with known or suspected food exposure
    - Submit diagnostic testing as indicated
    - Initiate prophylactic care as indicated

- Obtain a signed client authorization prior to release of medical information

TAURINE IN CATS – IS THERE STILL A CONCERN?

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Taurine (2-amino ethane sulfonic acid) is a well known essential nutrient of the cat. In the late 1980s Pion et al elucidated the role of taurine in feline dilated cardiomyopathy (DCM). Cats fed canned diets were at primary risk of feline dilated cardiomyopathy because taurine requirements in canned foods were nearly fourfold the published requirement and at least twofold greater than dry foods. The cause for the difference in taurine requirement based on food type is varied, however decreased protein digestibility related to canning has been demonstrated to have a primary role. Increased bacterial degradation of free and bound taurine in the intestine occurs with canned food feeding. Subsequent losses of taurine resulted in whole body depletion and DCM if sustained over months. Once recognized, pet food manufacturers quickly increased the crystalline taurine content of feline diets. Almost overnight, DCM, once common, became rare among cats. Reports of feline DCM occur sporadically but the concern regarding taurine deficiency appears long gone.

TAURINE PHYSIOLOGY

In addition to its role in cardiac function, taurine is also reported to be biologically important for normal retinal, neurologic, reproductive, immune, and platelet function, as well as, fetal development and growth. The largest pool of taurine in the body exists within the enterohepatic circulation where taurine is conjugated to bile acids forming bile salts critical to normal lipid absorption. Additionally, it functions as an antioxidant, neuromodulator, and osmolite. The molecular bases for these diverse actions remain unresolved.

Dietary taurine is absorbed in the gut by both active transporters and passive diffusion. The resorption of bile salts and free taurine within the enterohepatic circulation results in substantial taurine conservation and when disrupted can result in substantial taurine losses. Renal tubular resorption represents the major mechanism of taurine regulation within the body. Urinary taurine losses are greatest when dietary taurine exceeds the metabolic need, while excretion becomes minimal when the body pools are depleted or dietary levels are unable to sustain body. Thus, urinary taurine excretion plays a fundamental role in taurine homeostasis, particularly in the cat where it provides an early mode of conservation when dietary taurine becomes limiting.

NUTRITIONAL FACTORS AND TAURINE DEPLETION

A variety of nutrition factors contribute to taurine bioavailability and the potential for depletion. Taurine requirements in cats can vary based on differing protein source or processing method. Other factors include binding of bile salts by dietary fiber, peptides or resins; alteration in intestinal microbe numbers; or changes in bile salt enterohepatic recycling rate. Canned processing, Maillard reaction products (browning reaction), protein source, increased dietary fat, and rice bran have all been identified as nutritional factors that promote increased taurine loss. Meat source and certain vegetable proteins (soy protein) have also been shown to decrease serum taurine levels because of poor taurine bioavailability (eg, poultry meal), low taurine concentration (eg, rabbit or ground beef) or reduction of taurine resorption from the gut (soy protein). Grinding meat or allowing blood loss in the butchering process lowers taurine levels in the meat tissue. Case reports of taurine deficiency in cats fed raw meat diets without supplemented taurine have been described. With a new interest in feeding homemade diets or unconventional foods, veterinarians and consumers may need to consider these factors to assure adequate taurine nutrition.

DISORDERS CONTRIBUTING TO TAURINE LOSS

Most commonly, taurine deficiency has resulted from inadequate dietary intake coupled with alterations in metabolic conservation. Impaired renal function with amino aciduria can potentially contribute to increased taurine loss. Fortunately, quantities of taurine added to commercial foods are substantial and chronic renal insufficiency has not been associated with taurine depletion. Because normal bile flow and resorption influences whole body taurine status, disorders of bile resorption can increase taurine loss. Ileal resection or cholecystectomy increases bile salt loss into the feces with subsequent loss of taurine. Fortunately these disorders are uncommon and levels of dietary taurine appear adequate to account for this increased loss. Most importantly, chronic inflammatory bowel disease (IBD) has the potential to result in substantial taurine loss. Because IBD often contributes to small intestinal bacterial overgrowth, a combination of intraluminal taurine destruction combined with decreased taurine and bile salt absorption may contribute to taurine depletion.

CASE EXAMPLE

Two 8-month-old oriental shorthair cats were presented for chronic diarrhea. Physical examination revealed retinal degeneration and, in one cat, a murmur and gallop rhythm. Cardiac ultrasound revealed DCM in the kitten with a murmur. Fecal examination and culture using a pouch test revealed Tritrichomonas. Taurine deficiency was diagnosed based on chronic diarrhea and bacterial overgrowth and presence of retinal lesions typical of feline central retinal degeneration. Treatment included ronidazole for the Tritrichomonas infection and taurine supplementation to both cats. Six months following treatment cardiac function returned to normal, supporting the diagnosis of taurine-responsive DCM.

CONCLUSION

While commercial foods are supplemented with surfeit quantities of highly available taurine, cats eating unconventional diets or those with certain metabolic disturbances remain at increased risk of taurine deficiency.

THE SCOOP ON PLACING ESOPHAGOSTOMY TUBES IN CATS

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Enteral feeding is indicated in cats that cannot ingest adequate amounts of calories, but have sufficient gastrointestinal function to allow digestion and absorption of feeding solutions delivered into the gastrointestinal tract via an enteral feeding device. Esophagostomy tubes provide a relatively simple, safe, and cost-effective method for the administration of a variety of formulas and diets.

ESOPHAGOSTOMY TUBES

Esophagostomy feeding tubes are easily inserted, and insertion only requires light general anesthesia with isoflurane and intubation with a cuffed endotracheal tube. The technique is minimally invasive and no specialized endoscopic equipment is needed. Most feeding tubes today are made of polyurethane or silicone. These materials have tended to replace the older polyvinylchloride feeding tubes that tend to stiffen when exposed to digestive juices and are more irritating to patients, necessitating frequent tube replacement. Silicone is softer and more flexible than other tube materials with a greater tendency to stretch and collapse. Polyurethane is stronger than silicone, allowing for a tube of this material to have thinner walls and a larger internal diameter, despite the same French size. Both polyurethane and silicone do not rapidly disintegrate or embrittle in situ, providing a longer "wear". The French (F) unit measures the outer lumen diameter of a tube (one French unit is equal to 0.33 mm).

TECHNIQUE FOR ESOPHAGOSTOMY TUBE PLACEMENT

The patient should be placed in right lateral recumbency, and the left lateral cervical region clipped and aseptically prepared for tube placement. A 14- to 20-F red rubber catheter, silicone catheter, or polyurethane catheter should be premeasured from the mid-cervical esophagus to the eighth rib, and marked with a permanent marker to ensure the distal end of the catheter terminates in the distal esophagus. Three basic techniques for placement of a midcervical esophagostomy tube have been described.

Technique Using Curved Rochester-Carmalt, Mixter, or Schnidt Forceps

Advance the right-angle forceps into the mid-cervical esophagus from the oral cavity. Use the angle of the jaw and the point of the shoulder for landmarks to help ensure that the tip of the forceps can be palpated externally in the midcervical region. Push the curved tips of the Rochester-Carmalt forceps laterally at the mid-cervical esophagus, so they can be palpated below the skin. Use a No. 11 scalpel blade to make a stab incision through the skin only, exposing the subcutaneous tissue and muscle layers of the esophagus. Be careful to avoid the jugular and maxillofacial veins when selecting the stoma site. Exteriorize the tip of the forceps from the esophageal lumen through the skin incision. Guide the advancing forceps through the esophageal muscle layers and carefully dissect the esophageal mucosa off the tip of the forceps with a scalpel blade. Use the tip of the forceps to grasp the distal end of the feeding tube, and draw the tube out of the oral cavity. Secure the distal end of the feeding tube using the forceps to ensure that the tube remains exteriorized while the proximal end of the tube is pulled out of the animal's mouth. Retroflex the proximal tip of the feeding tube and advance it in an aboral direction across the pharynx and down the esophagus, while slowly retracting on the external end of the tube 20 to 40 mm. A wire guide can be used to facilitate pushing the proximal tip of the feeding tube into the esophagus. The exteriorized portion of the tube will be observed to rotate in a cranial direction as the tube moves down the esophagus, indicating correct placement of the tube in the esophagus.

Retention sutures (Chinese finger-knot suture) using 3-0 polypropylene are used to secure the distal end of the tube to the skin. An additional method of securing the tube involves passing a heavy suture on a taper needle through the skin next to the tube and into the periosteum of the wing of the atlas. Antibiotic ointment and gauze dressing is placed at the incision site, and the tube and entrance site is loosely bandaged with conforming gauze wrap. The correct placement of the tube in the mid-to-distal esophagus should be confirmed radiographically. It is important to ensure that the tube does not traverse the lower esophageal sphincter, as the tube can cause irritation, and predispose the patient to gastroesophageal reflux. Feeding can be instituted immediately following full recovery of the patient from anesthesia. The tube esophagostomy-skin interface should be examined at least daily during the first week for evidence of infection or leakage of food or saliva. The stoma site can be kept clean with a topical antiseptic solution (1:100 povidone-iodine solution in 0.9% saline). The tube can be easily removed once nutritional support is no longer needed by cutting the Chinese finger-trap anchoring suture and pulling the tube. The wound should be allowed to heal by second intention.

Percutaneous Feeding Tube Applicator Technique

An alternative tube esophagostomy technique utilizing an ELD percutaneous feeding tube applicator or similar device can be used. The applicator is inserted into the midcervical esophagus via the oral cavity. The distal tip is palpated, and an incision is made through the skin and subcutaneous tissue over the tip of the ELD. The trocar is advanced through the esophageal wall and directed through the incision. The distal end of the feeding tube is secured to the eyelet of the trocar with suture material. The ELD device and attached feeding tube are retracted into the esophagus and exteriorized out of the oral cavity. The feeding tube is redirected into the midcervical esophagus after inserting a wire stylet into the distal tip of the feeding tube. The tube is secured to the skin as mentioned above.

Percutaneous Needle Catheter Technique

This method incorporates the use of an esophagostomy introduction tube that is introduced into the midcervical esophageal area. The slot in the distal portion of the tube is palpated, and a Peel-away® sheath needle is introduced into the distal portion of the tube. The needle is removed from the sheath, and a 10-F catheter is introduced through the sheath to the distal third of the esophagus. The sheath is peeled away and the esophagostomy tube is carefully removed. The feeding tube is secured as described above. This technique has limitations as the small diameter of the feeding tube (10 F) only allows for the administration of fluids and liquid enteral formulas.

COMPLICATIONS

Despite the potential for esophageal scarring and stricture formation, esophageal stricture or a persistent esophagocutaneous fistula has not developed. The most common minor complication is peristomal inflammation, with peristomal abscessation occurring infrequently. Most of the inflammatory reactions are mild and respond to thorough cleansing with topical antibiotics. Other less common complications include regurgitation of the tube into the oral cavity and tube obstruction. Sucralfate and antacids have been reported to precipitate with enteral formulas and cause tube obstruction. Several "remedies" have been advocated to relieve tube obstruction. Warm water injected with gentle pressure and suction will relieve most bstructions. For more unyielding obstructions, carbonated water is instilled into the tube and allowed to sit for one hour before applying gentle pressure and suction. Pancreatic enzyme infusions and meat tenderizer have also been advocated to dissolve tube obstructions. On rare occasions, the passage of an angiographic wire down the lumen is needed to unclog the tube. Tube obstructions can be minimized by flushing the feeding tube with warm water before and after administering medications or enteral feedings. Elixir forms of medication should be used rather than crushed tablet forms whenever possible. Tablets should be crushed and dissolved in water prior to administration through the feeding tube, if no alternative form of medication is available.

CALCULATION OF NUTRITIONAL REQUIREMENTS

An estimate of the cat's nutrient requirements is needed to determine the minimum amount of food necessary to sustain critical physiologic processes. The resting energy requirement (RER) is the animal's energy requirement at rest in a thermoneutral environment and in a postabsorptive state. A linear formula can be applied to determine the RER of cats weighing at least 2 kg. Alternatively, one can utilize an allometric formula that can be applied to cats of all body weights (BW).

Linear formula: RER (kcal/day) = $(30 \times \text{BWkg}) + 70$

Allometric formula: RER (kcal/day) = $70 (\text{BWkg}^{0.75})$

Hospitalized patients should be fed at their calculated RER initially, realizing that their actual energy requirement is likely to change over the course of the disease process through recovery. Use of "fudge factors" extrapolated from the human literature to calculate the energy requirements of critically ill animals is discouraged, particularly in the early phase of nutritional support. Close observation of changes in body weight, physical examination findings (decreased subcutaneous fat stores, muscle wasting, and presence of edema or ascites), and ongoing losses (diarrhea, vomiting, exudative wounds), will help determine whether to increase or decrease the patients caloric intake.

Diet Selection

The type of formula to feed the patient will depend on the selected route of feeding, the functional status of the gastrointestinal tract, and the animal's nutrient requirements. Other factors, such as cost, availability, and ease of use may also be important. Commercial blended pet food diets are recommended for feeding via esophagostomy tubes. In select cases, the feeding of a liquid enteral formulation may be indicated. Feeding can be instituted immediately following esophagostomy tube placement once the animal has fully recovered from anesthesia. Diet can be administered as bolus feedings or continuous infusion when feeding via esophagostomy tube. Improved weight gain and decreased gastroesophageal reflux have been reported in human patients given continuous feedings, although similar studies are lacking in the veterinary literature.[8] Treatment with metoclopramide (1 to 2 mg/kg/24 hour as a continuous infusion) may be used to enhance gastric emptying and prevent vomiting. With bolus feeding, the required daily volume of food should be divided into four to six feeds. Animals are usually fed approximately 25% of their caloric requirement on the first day of feeding, with a gradual increase of 25% of the caloric requirement per day. Most patients are able to reach their energy requirement by the fourth or fifth day of feeding. The food should be warmed to room temperature and fed slowly through the tube to prevent vomiting. Flushing of the tube with 15 to 20 mL of lukewarm-warm water helps prevent clogging.

Esophagostomy Tube Removal

Unlike gastrostomy tubes, an esophagostomy tube can be removed the same day it is placed if necessary without concern for leakage and development of secondary complications. The dressing and sutures are removed while the tube is held in place. The tube is then occluded by kinking and pulled out using gentle traction. The ostomy site should be cleaned, antibiotic ointment applied, and a light dressing placed around the neck. The dressing should be removed in 24 hours, and the ostomy site inspected. The ostomy site should close within 24 to 36 hours. Skin sutures are not needed for closure of the ostomy site.

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HOW I TREAT CANINE SEVERE PANCREATITIS FROM A NUTRITIONAL PERSPECTIVE

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Severe pancreatitis is a serious illness in dogs. It occurs most often in middle-aged to older female dogs, and risk factors include obesity, diabetes mellitus, hyperadrenocorticism, and dietary indiscretion. Although the main focus of this article is the nutritional management of severe pancreatitis, a comprehensive approach to the diagnosis and treatment of this life-threatening disease is essential. Accordingly, important aspects of the diagnostic evaluation and non-nutritional treatment of affected dogs are also mentioned.

DIAGNOSTIC EVALUATION

Clinical signs in dogs with severe pancreatitis are anorexia, dehydration, abdominal pain, vomiting, diarrhea, and pyrexia. While most dogs are profoundly ill, the underlying cause of disease is not always immediately obvious. The minimum database for a dog suspected of having severe pancreatitis should include a complete blood count, coagulation profile with D-dimers, biochemical profile, urinalysis, chest and abdominal radiographs, and abdominal ultrasonography. Serious concurrent conditions are often present and may include bacterial infection or sepsis; disseminated intravascular coagulation; severe hypoproteinemia; acute renal failure; hyperglycemia; and, profound hyperlipidemia.

NUTRITIONAL THERAPY

The three primary goals of nutritional therapy for severe pancreatitis in dogs are 1) to completely rest the bowel and allow inflammation to resolve; 2) to meet requirements for essential nutrients while the intestinal tract is nonfunctional; and 3) to successfully transition the animal to a well-tolerated oral diet once inflammation has subsided.

Complete Bowel Rest

Complete bowel rest has traditionally been accomplished in dogs with severe pancreatitis by withholding all food and water. Lack of food in the gut decreases pancreatic stimulation and secretion of enzymes, helping to stop the cycle of injury and inflammation that characterizes the disease. The period over which the animal is held without oral intake varies but may be a week or more, depending on the severity of disease. Intravenous crystalloids are typically administered to maintain hydration. While this may accomplish the goal of complete bowel rest, it does nothing to supply nutrients. This is a problem, since inadequate protein and energy intake during critical illness can lead to life-threatening protein-calorie malnutrition. Protein-calorie malnutrition occurs when essential requirements for energy and proteins are not met, forcing the animal to catabolize endogenous stores. The degree of catabolism is proportional to the severity of illness: the sicker the animal, the more quickly stores are consumed. Accessible energy stores are rapidly depleted, and crucial visceral proteins as well as essential enzyme systems are broken down. Cardiovascular, respiratory, gastrointestinal and immune functions are all compromised, ultimately causing multiple organ failure and death. Seven to 10 days of complete food deprivation in a critically ill dog with severe pancreatitis is sufficient to cause serious protein-calorie malnutrition.

A superior approach is to rest the gut and provide nutritional support at the same time. There are two ways to accomplish this: by feeding intravenously (parenteral nutrition), or by using a jejunostomy tube to access the functional gut, bypassing the diseased proximal segment (enteral nutrition). Both techniques have advantages and disadvantages. Parenteral feeding completely bypasses the gut, and the dedicated intravenous catheter needed can usually be placed quickly and without general anesthesia. On the other hand, lack of food within the intestinal tract during parenteral feeding causes gut mucosal atrophy and compromises intestinal immune function, putting the animal at risk for bacterial translocation and sepsis. Enteral feeding is more effective in maintaining gut health, and actually promotes healing of underlying intestinal disease. Unfortunately, jejunostomy tubes are usually placed through exploratory laparotomy, a procedure that may be too risky when severe pancreatitis is associated with hemodynamic instability and coagulopathy. In the end, the advisability of exploratory laparotomy is the primary consideration that determines whether a dog with severe pancreatitis is fed with a jejunostomy tube, or parenterally. If the diagnosis is certain and the animal is stable, or if there is another indication for surgery (such as a pancreatic abscess), then the advantages of using the gut through a jejunostomy tube are compelling and this is probably the best choice. Alternatively, if the animal is unstable and the only reason for surgery is to place the tube, then parenteral feeding is probably the more practical option. However, enteral feeding should be resumed as soon as possible to promote the reestablishment of normal intestinal function.

Meet Essential Nutrient Requirements

Before parenteral or jejunostomy feedings are initiated in a dog with severe pancreatitis, it is essential that the animal be stabilized by correcting all fluid balance, acid-base and electrolyte abnormalities. Administering nutrients to a marginally hydrated and hypotensive animal with significant acid-base abnormalities from intractable vomiting can cause serious metabolic complications. Aggressive supportive care including intravenous crystalloids with added electrolytes, synthetic colloids, broad spectrum antibiotics and fresh frozen plasma is often necessary. Fluid balance in dogs with evidence of acute renal failure must be monitored with great care, by precisely measuring volume of intravenous fluids administered as well as the volume of urine produced ("ins and outs"). Antiemetics are helpful in many cases, and analgesics should be routinely considered as well. The author prefers a continuous rate intravenous infusion of fentanyl, because it is effective and the dose can be quickly, easily and safely manipulated due to the drug's short half-life.

Dogs with severe pancreatitis are generally able to start nutritional support within 24 hours of admission to the intensive care unit. The decision to initiate feeding should be made as early as possible in the course of disease: the longer the delay, the worse underlying protein-calorie malnutrition will become and the harder it will be to reverse. A parenteral prescription is designed or a tube feeding ration is selected that meets the animal's essential nutritional requirements. Not all nutrients are essential for an adult dog that was basically healthy prior to the current acute illness, especially if the expected duration of support is likely to be 1 to 2 weeks at most. The list of nutrients that must be specifically considered is actually quite short: calories (including both carbohydrate and lipids), protein, electrolytes, phosphorus and the water soluble B vitamins. Dogs with severe pancreatitis should be fed conservatively with respect to the total number of calories provided, with the target at or just slightly above the resting energy requirement (RER). Overfeeding calories causes cholestasis, hepatic lipidosis, respiratory failure and hypermetabolism in people, and should be avoided in dogs as well. It is better to start with a conservative energy intake and gradually increase it if necessary. The proportion of calories provided as carbohydrate versus lipid must also be carefully considered. Large doses of intravenous lipid emulsion are obviously contraindicated in hyperlipidemic dogs with pancreatitis, because lipid particles may cause further pancreatic injury. However, simple carbohydrates may not be well tolerated either, especially if endocrine pancreatic function has been compromised by severe or recurrent inflammation and necrosis. A combination of lipid and carbohydrate calories is indicated in most dogs, with the exact ratio depending on individual tolerance.

Critical illness is associated with increased protein requirements, and in dogs with severe pancreatitis these are often superimposed on significant hypoproteinemia. However, it is best to be conservative with protein intake as well, to avoid complications such as hyperammonemia and azotemia. Troublesome complications of hypoproteinemia such as peripheral edema are best managed with synthetic colloids. Albumin synthesis is rarely rapid enough to reverse clinical signs quickly in severely affected animals in any case, even with nutritional support. Plasma transfusion also tends to be an ineffective treatment for hypoproteinemia in all but the smallest dogs. Even though plasma is definitely indicated in severe pancreatitis to supply clotting factors for the treatment of disseminated intravascular coagulation and also to supply α-macroglobulin to bind circulating proteases, it is not an effective or practical treatment for hypoproteinemia. Very large volumes are required because infused albumin equilibrates with the extravascular space within only a few hours.

Finally, dogs being treated for severe pancreatitis must have adequate intake of sodium, potassium, chloride, magnesium, and phosphorus as well as the water soluble B vitamins. Deficiencies of potassium, magnesium and phosphorus are arguably most problematic: phosphorus deficiency in particular can lead to refeeding syndrome, which is characterized by profound hypokalemia, hypophosphatemia, glucose intolerance, and hemolysis. Cardiovascular collapse and death are possible in severe cases. Baseline levels of most minerals and electrolytes plus B vitamins are supplied in parenteral prescriptions or tube feeding formulations. Use of the intravenous crystalloid solutions already being received by the animal to make hour by hour adjustments in minerals and electrolytes tends to be more convenient and less frustrating since it avoids the need for repeated reformulation of the feeding solution.

Parenterally fed dogs with severe pancreatitis should receive individualized prescriptions based on the principles outlined above. When a jejunostomy tube is used, it is generally much more convenient to use the commercial tube-feeding ration that most closely meets the desired profile. The small bore of jejunostomy tubes means that liquid diets must be used. Complete and balanced liquid polymeric veterinary products are available (CliniCare Canine/Feline, Abbott). Partially digested liquid monomeric human products (Vivonex HN, Novartis) may be absorbed more efficiently but are not balanced for use in dogs, tending to be lower in protein while relatively high in carbohydrate.

Transition to Oral Diet

Oral feeding should be resumed as soon as it is tolerated. Very small amounts of a bland, low residue, highly digestible ration that has a low to moderate fat content should be offered 4 to 6 times a day. Prescription gastrointestinal diets fit these criteria and can be fed indefinitely if needed. In some cases, more significant dietary fat restriction is recommended in an attempt to prevent recurrent episodes of pancreatitis. Some of the most fat-restricted commercial products available for dogs are intended specifically for weight reduction, but these must be used with care when weight loss is not the goal: close monitoring is necessary to make sure optimal body condition can be maintained. Also, there is no indication for the high fiber content of some of these products when treating pancreatitis. A better choice may be Royal Canin Canine Low Fat™, a prescription product that is low in both fat and fiber content, and balanced for long term use.

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FEEDING TUBES IN SMALL ANIMAL PRACTICE

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Nutritional support is required for anorexic patients, debilitated patients, patients in a high catabolic stage (peritonitis, sepsis, burns), or stressed patients (surgical patient). Nutritional support allows a faster soft tissue healing, a better immune system response and a faster recovery from the patient. Nutritional support can be performed with food intake stimulation, force feeding, and feeding tubes. Vitamin B, valium (0.2 mg/kg IV) and ciproheptadine (2 mg/cat 2 to 3 times a day) have been used to stimulate food intake in dogs and cats with variable results. Force feeding with a syringe or tube is possible for one day or two. Force feeding places lot of stress on the animal and may induce aspiration pneumonia. Feeding tube placed either surgically or under endoscopy is the most efficient technique to provide nutritional support to a patient. Feeding tubes can be easily placed at the end of an abdominal surgery and may avoid lot of complications and troubles after surgery.

NASOGASTRIC TUBE

A nasogastric tube can be placed in dogs and cats if feedings need to be continued for more than 2 days. It is a good technique for the nutritional support of young animals. It does not require general anesthesia for its placement. A topical anesthetic (bupivacaine: 2 to 5 drops) is placed into the nostril. Before placing the tube, the distance from the nares to the stomach needs to be measured. The stomach is located at the level of the last rib. A 3.5 French tube is recommended for puppies and kitten, while a 5.0 Fr tube can be used for adult cat and dogs less than 8 kg. With the animal's head held in a normal static position the tube is introduced in the nose in a caudo-medial direction ventral to the alar fold. Pushing the nose upward helps moving the tube downward in the ventral meatus. A stylet or guide wire might be useful to guide the tube in the correct direction. The tube progress through the larynx into the esophagus and the stomach. If the animal is coughing, the tube is more likely going into the trachea. A bolus of sterile saline can be injected in the tube. If the animal coughs more likely the tube is in the trachea. If there is any doubts on the placement of the tube radiographs should be taken to confirm the placement of the tube in the stomach and not the trachea. Palpation of the trachea and the tube in the esophagus is a good indication for correct placement of the nasogastric tube. Since the tubes are small in diameter a liquid diet (Clinicare) is recommended. The tube needs to be flushed between feeding to prevent the tube from plugging.

ESOPHAGOSTOMY TUBE

Several techniques have been described for placement of an esophagostomy tube placement in dogs and cats. The animal needs to be under general anesthesia. The entire left cervical region from the ventral to dorsal midline need to be clipped and prepared for surgery.

The left side of the cervical region is draped and a percutaneous feeding tube applicator (ELD Gastrostomy tube applicator) is inserted through the mouth in the proximal cervical esophagus. The tip of the ELD device is turned outward and the cervical tissue are tented up. A small skin incision is made just large enough to accommodate the feeding tube. The incision is made deeper to the esophagus and the sharp needle in the ELD is advanced to puncture through the esophagus. A feeding tube is attached to the needle. The needle is retrieved in the ELD device. The ELD device is retrieved through the mouth with the feeding attached. Now the feeding tube is going through the skin of the left cervical area, the esophagus, and exiting in the mouth. The tip of the tube is then redirected into the pharynx and the esophagus. The tube needs to be manipulated gently to prevent perforation of the distal esophagus. The tube is then secured with a Chinese finger trap suture. A light bandage is applied to protect the tube. The tip of the tube should be in the esophagus. It is then necessary to measure the length of the tube that could be placed in the esophagus without entering the lower esophageal sphincter. The lower esophageal sphincter is located at the level of the xyphoid. A large red rubber feeding tube can be placed with this technique. For a cat, a 12 to 14 Fr tube can be placed and for a 30-kg dog a 20 Fr tube be used. It is recommended to increase the diameter of the hole at the tip of the tube to prevent obstruction of the tube with food.

An alternative technique is to use a large Carmalt or curve forceps for the placement of the tube instead of the ELD device. Forceps have a tendency to create a hole too large in the esophagus, which may result in leakage of saliva and food around the tube. It will induce a severe cellulitis, and abscess formation.

Blenderized food can than be used for the nutritional support of the patient. The animal is usually fed 4 times a day. The tube needs to be flushed after each feeding with copious amount of water. Tubes entering the stomach will induce vomiting. Some dogs or cats have been vomiting their tube.

GASTROSTOMY TUBE

Gastrostomy tubes are more commonly placed during abdominal exploration. However, they can be placed with a limited flank approach or percutenously with an endoscope.

Surgical Technique During Abdominal Exploration

The greater curvature of the body of the stomach is identified. The greater curvature of the body of the stomach is manipulated to identify the are with e least amount of tension after placement against the left abdominal wall behind the last rib. A purse-string suture with 3-0 monofilament absorbable suture is placed in the gastric fundus in the identified area (Figure 1 B).

A Foley catheter (18 to 20 French) is inserted first through the left abdominal wall just behind the last rib (Figure 1 A). A stab incision is made in the middle of the purse-string suture and the tip of the Foley introduced in the stomach (Figure 2 C). The balloon of the Foley catheter is inflated with appropriate amount of saline and the purse-string suture tied. Four gastropexy sutures (3-0 monofilament absorbable material) are placed between the stomach wall and the abdominal wall (Figure 2 D-E). The sutures are evenly distributed around the Foley catheter. A Chinese finger tap suture is placed around the Foley catheter on the skin.

Flank Approach

After surgical preparation of the left flank, a rigid stomach tube is inserted through the mouth into the stomach. The stomach tube is rotated to tent up the skin of the left flank. With the tube maintained in place a skin incision is performed over the tube. Blunt dissection of the abdominal wall is performed over the tube. When the peritoneum is opened, the stomach wall is identified on the top of the tube. The stomach wall is then pexied to the abdominal wall with four mattress sutures.

The stomach can then be removed. A purse-string is placed in the stomach wall and a Foley catheter is introduced after puncture with an #11 blade in the middle of the purse-string. The purse-string is tight and the skin closed. The Foley catheter can be tunneled under the skin before it penetrates in the stomach.

Percutaneous Endoscopic Gastrostomy Tube Placement

Percutaneous endoscopic gastrostomy (PEG) tubes are inserted with the aid of general anesthesia. The animal is placed in right lateral recumbency and the flank area behind the last rib is surgically prepared. The endoscope is introduced in the stomach through the mouth. The stomach is insufflated with carbon dioxide. The stomach wall is then getting in contact with the abdominal wall. The lighted tip of the endoscope is turned to visualize the wall of the body of the stomach. A large needle is inserted into the stomach under the control of the endoscope. A nylon suture is inserted in the needle and grabbed in the stomach with a grasper inserted through the endoscope. The suture is pulled through the mouth while the endoscope is withdrawn. A mushroom tip catheter is then attached to the nylon suture coming out through the mouth. The lubricated catheter is pulled into the stomach by the suture exiting the body wall. Resistance will be encountered when the tip of the catheter hit the stomach/body wall. Firm traction is applied o the suture and counter-traction is applied to body wall to be able to pull the catheter through. A rubber flange is fitted down the tube to prevent slippage of the tube. The flange is glued to the catheter.

The tube can be removed by applying firm traction of the tube that will collapse the mushroom. In large breed dog the mushroom can be cut and pass through the feces.

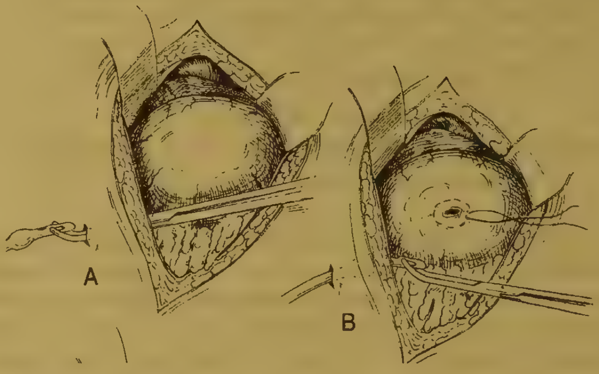

Figure 1. A and B.

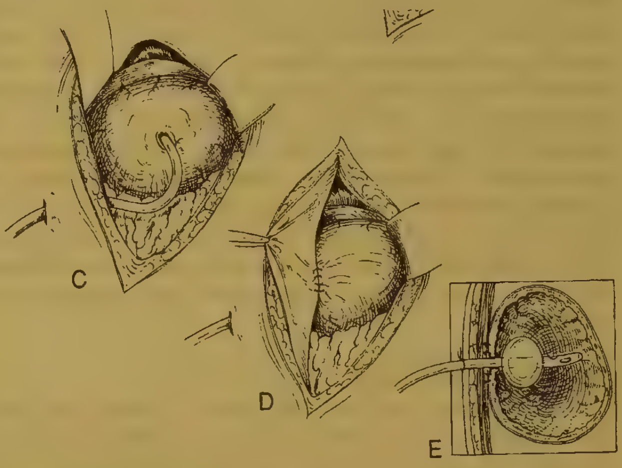

Figure 2. D, E, and F.

The gastrostomy tube is removed by cutting the Chinese finger trap, deflating the balloon and pulling the catheter. Very often, the balloon is ruptured after 2 weeks because of the acid content of the stomach. If the tube needs to be maintained for more than 2 weeks a mushroom tip catheter is preferred to a Foley catheter. The fistula between the stomach and the skin is going to close quickly. Usually there is no leakage of stomach content through the fistula.

Feeding is started 24 hours after placement of the gastrostomy tube. Leaks of food can occur around the tube if the feeding is started to early. The correct amount of gruel for the patient is administered through the catheter. The catheter needs to be flushed every 4 hours to prevent its obstruction. The tube needs to stay in place for at least 7 days before its removal to allow appropriate sealing of the pexy. The gastrostomy tube can be kept for several weeks. It is recommended to start feeding with 1/4 maintenance and to increase the caloric intake by 1/4 every day. If animal shows abdominal discomfort, vomiting or diarrhea the caloric intake is decreased by a 1/4. The amount of food required daily is divided in four feedings.

JEJUNOSTOMY TUBE

A jejunostomy tube is placed when bypass of the upper part of the gastrointestinal is required. A loop of jejunum is selected distal to the part of the intestine that needs to be bypassed. A purse-string of 3-0 monofilament absorbable suture is placed on the antimesenteric border of the jejunum. The jejunostomy tube (3 to 5 French) is first inserted through the abdominal wall. A stab incision is made in the middle of the purse-string and the jejunostomy tube is introduced in the jejunum 20 cm aborally. The purse-string is tied. Then, four jejunopexy sutures are placed evenly around the jejunostomy tube between the abdominal wall and the jejunum.

Feeding can be started immediately after placement of the jejunostomy tube. A liquid diet is administered continuously through a feeding pump. The catheter needs to be flushed every 4 hours to prevent its obstruction. It is recommended to start feeding with 1/4 maintenance and to increase the caloric intake by 1/4 every day. If animal shows abdominal discomfort, vomiting or diarrhea the caloric intake is decreased by a 1/4. The tube needs to stay in place for at least 4 days before its removal to allow appropriate sealing of the pexy. Usually, the jejunostomy tube is for short-term usage because a pump is required to deliver the diet. Jejunostomy tube is advantageous for patients requiring multiple anesthesias (open abdominal drainage) or being profusely vomiting before surgery.

GASTRO-JEJUNOSTOMY TUBE

It is very common to place a gastrostomy and a jejunostomy tube at the time of surgery. The jejunostomy tube is for the short-term support of the vomiting patient and the gastrostomy tube for the long-term support of a severely debilitated patient. The gastrostomy is placed first as described earlier during an abdominal exploration. Then a jejunostomy tube is fed in the lumen of the gastrostomy tube into the duodenum and the proximal jejunum. The gastrostomy tube has to be of a large diameter (22 to 24 gauge) to allow passage of the jejunostomy tube. The gastrostomy tube can then be used to aspirate stomach content to prevent vomiting and the jejunostomy tube can be used for feeding of the patient. When the animal is not vomiting, the feeding can be performed through the gastrostomy tube. The jejunostomy tube can then be removed. The advantage of this technique is that only one opening is required for the placement of the two feeding tubes. Gastro-jejunostomy kits are available. Each tube is managed as each tube placed separately.

FIBER FOR GI HEALTH

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The gastrointestinal tract (GIT) in dogs is a very dynamic organ that performs numerous functions essential for health and well-being. For example, a critical function of the GIT is digestion and absorption of nutrients, as well as elimination of potentially harmful substances and waste products. In addition, the GI tract is the most voluminous immunological organ in the body and also functions as an endocrine organ.

Although the effect of various nutrients on the GIT in dogs has been studied for decades, it is only in the past 10 to 15 years that significant knowledge and understanding of the role that dietary fiber has in maintaining health and preventing diseases has been recognized. Historically fiber has not been considered essential in the diets of dogs, but more and more the critical role that fiber has in promoting a healthy GIT is being recognized. The role of fiber in the GIT can be generally summarized as having three different effects: 1) physical, 2) fermentative, and 3) bacterial.

INTRODUCTION OF DIETARY FIBER

Dietary fiber was originally defined as "the remnants of plant cell walls not hydrolyzed by the alimentary enzymes of man," but the definition was subsequently modified to include all plant polysaccharides and lignin, which are resistant to hydrolysis by digestive enzymes. More recently, the definition of fiber has been modified further and is now defined as the composite of all dietary constituents that are not digested by endogenous enzyme secretions in mammals. Although not digestible, dietary fiber is considered to have nutritional value because of its importance in maintenances of the functional integrity of the GIT.

Dietary fiber consists of material of diverse chemical and morphological structure. Large differences exist in the physical form and the physiologic effect of various classes of dietary fiber in dogs, and it is now recognized that specific fiber types can be utilized for specific effects on the GIT. Major components of dietary fiber include nonstarch polysaccharides, cellulose, hemicellulose, mixed-linkage beta-glucans, pectins, gums, and mucilages. Lignins are also included in the estimates of total dietary fiber because they are plant cell wall constituents which can greatly affect the digestibility of plant-derived foods. Quantitatively, lignins do not make a significant contribution to total dietary fiber intake unless intact seeds are consumed.

The diverse nature of fiber has lead to numerous ways of classifying fiber, including by solubility in water, rate of fermentation, digestible and indigestible fractions, water-holding capacity, viscosity, fecal-bulking ability, cation exchange capacity, bile acid-binding ability and microbial fuel value. These numerous classifications of fiber have lead to confusion since fibers classified in the same category in one system may be classified in entirely different categories in another system.

In the past, dietary fiber has been classified by its solubility (soluble vs insoluble). This classification is based on how fiber reacts with water. All fibers hold water to some degree, however, the soluble fibers have a greater water holding capacity than insoluble fibers, and they may form gels and viscous solutions in the GIT (Table 1). In more recent years, this classification of fiber has fallen into disfavor. Categorization of fiber types based on fermentability (Table 1) is a more meaningful way to describe certain fiber sources for dogs because the fermentability or the capacity for fiber breakdown by intestinal bacteria more accurately assesses fiber's potential beneficial effects in the GIT than does solubility.

Table 1. Dietary Fiber Fermentation in Dogs

Fiber Type	Solubility	Fermentability
Beet pulp	Low	Moderate
Cellulose	Low	Low
Rice bran	Low	Moderate
Gum arabic	High	Moderate
Pectin	Low	High
CM-cellulose	High	Low
Methylcellulose	High	Low
Cabbage fiber	Low	High
Guar gum	High	High
Locust bean gum	High	Low
Xanthan gum	High	Moderate

BENEFICIAL EFFECTS OF FERMENTATION OF FIBER BY INTESTINAL BACTERIA

Fiber usually passes through the stomach and small intestines intact in dogs because dogs do not endogenously produce the enzymes needed to digest fiber. Until recently, fiber fermentation was thought to be irrelevant in dogs. However, once fiber reaches the large intestines of dogs, intestinal bacteria are able to ferment certain types of fiber, resulting in the production of short-chain fatty acids (SCFAs). As a result, fermentation of fiber is very important in dogs. The major SCFAs produced from fermentation are acetate, propionate, and butyrate. In ruminants and herbivorous animals, SCFAs provide a significant source of energy [ie, up to 75% of daily energy requirement (DER)] to these species. However, dogs have a relatively short and simple structure of the large intestines, and as a result, SCFAs provide less than 5% of energy needs and therefore have little effect on energy balance in dogs.

Although production of SCFAs in the large intestines of dogs provides very little energy, it does have a number of beneficial effects which include:

An energy source for colonocytes. Colonocytes derive more than 70% of their energy needs from luminally derived SCFAs. As a result, fermentation of fiber provides a readily available source of energy for colonocytes that aids in maintaining the health and function of these cells. SCFAs are also important for cell renewal and repair. Epithelial cells of the GIT turnover rapidly and must be replaced on average once every three days. By providing energy for intestinal cells, SCFAs facilitate the replacement of cells that have been sloughed during the normal process of cell turnover.

Maintenance of normal intestinal electrolyte and fluid balance. SCFAs facilitate the absorption of sodium, chloride and water in the colon. For example, a study in dogs showed that sodium and SCFA absorption could account for the entire osmotic absorption of water from the colon. As a result, providing fermentable fiber in the diet is essential in maintaining the normal homeostatic absorptive function of the intestine of dogs.

Maintenance of intestinal motility. Normal intestinal motility appears to be influenced by the presence of SCFA. Kamath et al infused bolus doses of physiological concentrations of SCFA into the ileum of dogs. As the dose of SCFA increased, ileal motility increased. Therefore, providing fermentable fiber in the diet may be important in maintaining normal intestinal motility.

Amelioration and prevention of pathogenic bacterial overgrowth. Harmful bacteria (eg, Clostridia, salmonella, Enterobacteria) can produce 1) toxins, 2) carcinogens, and 3) putrefactive substances. Beneficial bacteria (eg, Bifidobacteria, Lactobacilli) 1) inhibit the presence of harmful bacteria, 2) stimulate immune function, 3) aid in digestion and (or) absorption of food, and 4) synthesize vitamins. Maintenance of beneficial indigenous bacterial populations is important in prevention of pathogenic bacterial overgrowth in the intestine. Indigenous bacterial populations in the dog GIT ferment certain fiber sources that result in the production of SCFA. The presence of SCFA inhibits the growth of pathogenic bacteria. As a result, not only are indigenous bacterial populations necessary for the production of SCFA, but they can also directly inhibit pathogenic bacterial overgrowth in the gut. A growing body of evidence supports the theory that certain dietary fiber sources can modify the composition of the intestinal microflora.

Maintenance of optimal colonic morphology. Dogs fed a fermentable source of fiber had increased colon weights, increase mucosal surface areas and mucosal hypertrophy compared to dogs fed a nonfermentable fiber source (cellulose). These effects on the colon also aid recovery after intestinal surgery.

Amelioration of intestinal inflammation. Diets containing nonfermentable fiber (cellulose) as the sole source of dietary fiber fed to dogs resulted in a higher incidence of mucus distension and cryptitis when compared with similar diets that contained a fermentable fiber source.

ALL FERMENTABLE FIBERS ARE NOT CREATED EQUAL

Fiber sources can vary in their level of fermentability in dogs (Table 1). As fermentation rate of fiber increases, GI transit time decreases, fecal bulk decreases and fecal bile acid excretion increases. Fibers with low fermentability (eg, cellulose, methylcellulose, oat fiber, peanut hulls, xanthan gum, locust bean gum) are not metabolized by intestinal bacteria to produce SCFAs. Rather they retain their structure while passing through the GIT intact and act as bulking agents. Highly fermentable fibers (eg, pectin, guar gum, pectin) are rapidly metabolized by intestinal bacteria. One of the products from bacterial fermentation of fiber is SCFAs. However, less desirable substances are also produced from bacterial fermentation, including carbon dioxide, hydrogen, and methane. If a fiber source is rapidly fermentable, large amounts of gases will be rapidly produced in the colon, resulting in diarrhea and cramping. Moderately fermentable fiber sources (eg, beet pulp, rice bran, gum arabic, xanthan gum) produce SCFAs without resulting in rapid production of gases and associated diarrhea. Therefore, moderately fermentable fiber produces the beneficial effects associated with production of SCFAs occur without the undesirable effects seen with rapidly fermentable fiber.

An ideal fiber source for dogs should contain a moderately fermentable portion to facilitate SCFA generation, as well as a nonfermentable portion to provide bulk and enhance peristalsis. Beet pulp fulfills both of these requirements.

What is Beet Pulp?

Beet pulp is the fiber material that remains after sugar is extracted from sugar beets. Beet pulp is not derived from red beets; therefore, there is not anything in sugar beet pulp that can affect coat color of dogs. It has been widely used in the livestock industry for many years, and in the last 10 years, the use of beet pulp has expanded into the pet food industry as a source of fiber. It is a safe fiber source and contains no known toxins.

FIBER AS A SOURCE OF PREBIOTICS TO ENHANCE INTESTINAL HEALTH

Prebiotics have received a lot of attention recently as a way to modulate bacterial populations in the colon to favor beneficial bacterial. Prebiotics are defined as nondigestible food ingredients that beneficially affect the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon.

Fructooligosaccharides (FOS)

Certain fermentable fiber sources, such as FOS, are good sources of prebiotics in dogs, and the proportion of different bacterial species is related to the type of fermentable substrate available. Fructooligosaccharides are found naturally in many different foods, including plants like beet root (after pulp processing), soy (in the hulls), psyllium, chicory (after hydrolysis) and numerous other fruits, vegetables and grains. They can also be synthesized commercially. Beneficial intestinal bacteria (ie, lactobacilli and bifidobacteria) use fermentable fiber as a metabolic fuel, whereas pathogenic bacteria (i.e. salmonella, *Escherichia coli, Clostridium perfringens*) cannot metabolize FOS for energy. Production of SCFAs from fiber by beneficial bacteria also lowers colonic pH, further impeding the growth of bacterial pathogens. As a result, in the presence of FOS, beneficial bacteria thrive, multiply, and crowd out pathogenic bacteria. In addition, a study by Willard, et al showed that supplementing the diet of dogs with FOS resulted in a significant decrease in the number of aerobic and anaerobic bacteria in the small intestine. This too prevents excessive numbers of pathogenic bacteria from invading the small intestines.

Mannanoligosaccharides (MOS)

Mannanoligosaccharides are unique fiber sources similar to FOS. The difference between FOS and MOS is that fructose is the predominant sugar molecule in FOS, whereas mannose is the predominant sugar molecule in MOS. Mannanoligosaccharides are natural fibers found in yeast cells, and they use a different mechanism to prevent the growth of harmful bacteria in the GIT than do FOS. One way pathogenic bacteria establish themselves in the GIT is by attaching to the intestinal wall and colonizing the GIT. Pathogenic bacteria are able to attach to the intestinal wall because they have finger-like projections, called fimbriae, that allow them to bind to specific residues (eg, mannose) on intestinal cells. Since MOS contains mannose, fimbriated mannose-specific pathogens can bind to MOS instead of the intestinal wall. By preventing these bacteria from adhering to the intestinal wall, MOS can inhibit the growth of pathogenic organisms, reduce their effects in the GIT and aid in the excretion of these harmful bacteria. They are very effective in preventing diarrhea and contribute to the prevention of digestion-related infectious diseases.

FOS and MOS Enhance the Effectiveness of the Gastrointestinal Immune System

The GIT contains a large population of bacteria, and it is critical to the health of dogs that these bacteria remain in the gut and are prevented from translocating systemically. The GIT is constantly under antigenic stimulation from both bacteria and food, and the integrity of the GIT is essential for maintenance of intestinal health.

The gut contains both non-immunological barrier defenses and immunological barrier defenses. Non-immunological barriers include 1) the anatomy of the gut (intact microvilli and tight junctions between cells), 2) peristalsis and mucus, which makes it difficult for pathogens to attach and enter cells, 3) low pH of gastric secretions, 4) digestive and bactericidal enzymes secreted by the stomach, pancreas and epithelial cells to inhibit the attachment and growth of bacteria.

The gut is also the largest immunological organ in the body. As a result, immunological barriers play a critical role in maintaining normal health and function of not only the GIT but systemically as well. Gut associated lymphoid tissue (GALT) is composed of cells residing in the lamina propria regions of the gut, intraepithelial lymphocytes interspersed between epithelial cells, and immune cells located in organized lymphatic tissue (Peyer's patches and mesenteric lymph nodes).

Fermentable fibers, such as FOS, can have a major impact on the gut's immune function. In a study by Field, et al, dogs were fed isonitrogenous, isoenergetic meat-based diets supplemented with either a combination of fermentable fibers (beet pulp, gum arabic and FOS) or with nonfermentable fiber (cellulose). Each diet contained similar amounts of fiber but differed in its fermentability. The diet supplemented with fermentable fiber significantly ($P<0.05$) decreased the proportion of Ig+ cells and increased the CD4/CD8 (ie T-helper cell : cytotoxic T-cell ratio) in peripheral blood. Therefore, adding fermentable fiber to the diet of dogs changed the composition and function of immune cells in GALT.

CONCLUSIONS

Fiber is not considered an essential nutrient in dogs, and with the exception of insoluble fiber, such as cellulose, was largely ignored in the diet of dogs until the last 10 to 15 years. More and more studies are supporting the important role of dietary fiber for maintaining gastrointestinal and systemic health. Specific fiber types are being used to cause specific affects on bacterial populations in the gut, as well as systemic affects on the immune system. As more studies are conducted in dogs demonstrating the number of beneficial effects different fiber types (fermentable vs nonfermentable) have on GIT health, fiber may one day be classified as an essential nutrient in dogs.

References are available from the author upon request.

NUTRITION TO PROMOTE HEALTHY MOBILITY

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Optimal nutrition to support healthy mobility is important across the lifespan. Each life stage has nutritional aspects of particular significance.

PUPPY NUTRITION FOR HEALTHY MOBILITY

Across breeds of dogs from the Chihuahua to the Great Dane, there is an immense range of mature body size, though dogs on either end of this spectrum reach mature body size in about the same period of time. If allowed to grow at their genetic potential large breed dogs are put at particular risk for development skeletal problems. While genetics plays a role in the development of skeletal abnormalities, nutritional management plays an important role in the expression of this genetic programming. Controlled growth rate is important to reduce development of skeletal problems including hip dysplasia, osteochondroses, and hypertrophic osteodystrophy, particularly in large breed dogs. Nutrition can play a key role in decreasing the occurrence and severity of these abnormalities.

- Controlled growth rate via controlled energy intake optimizes bone strength and conformation during development and limits mechanical forces from body weight during critical joint development. A diet with 14% fat provides enough calories for growth but keeps it below maximum growth rate.
- Take care not to overdo mechanical forces on joints resulting from activity or training. Keep activities low impact.
- Dietary protein has little impact on skeletal disease. A diet with about 26% support growth and development in a slightly reduced energy density diet (~14% fat)
- Dietary calcium and phosphorus concentrations of 0.8 to 0.9% and 0.67%, respectively, result in fewer skeletal abnormalities while supporting attainment of maximum stature and bone density.
- With carefully balanced diets avoid calcium supplementation, which can increase the incidence of certain developmental bone diseases. Any supplementation whether as calcium, bone meal or dairy products will increase the calcium intake and increase the puppy's likelihood of developmental bone disease.

ADULT NUTRITION TO SUPPORT HEALTHY MOBILITY

Even if a dog or cat does not get optimal nutrition during development there are a number nutritional avenues to improve their mobility in adulthood. One of the most influential factors affecting mobility and the progression of skeletal disorders is overall body weight. Obesity is recognized as an important factor in the expression of osteoarthritis in humans. Obesity in dogs and cats has been estimated at 25% or higher. Dogs and cats with mobility problems are likely to be more sedentary and as a result often carry more excess weight.

During the adult years, maintaining optimum body weight can help reduce development and progression of a number of disease conditions including osteoarthritis. If owners fail to maintain optimal body with of their pet's one of the most rewarding interventions can be the implementation of effective weight loss programs. Reducing weight in overweight dogs with hip osteoarthritis has been shown to improve mobility.

- Weight loss alone can have very noticeable benefits in improving mobility.
- Improvements in mobility can also serve as powerful motivators to help ensure owner compliance with the weight loss program for their pet.
- Coupling exercise and/or physical therapy with caloric restriction weight loss programs can help achieve even better weight loss and improvements in mobility

SENIOR NUTRITION TO SUPPORT HEALTHY MOBILITY

As with adult dogs, body weight, in addition to the physiologic and metabolic changes associated with aging can affects health and well-being in senior dogs. The risk of joint conditions increases as dogs reach the senior life stage. Osteoarthritis can be a common and debilitating problem for senior dogs, but can be managed by a combination of weight control, exercise, and drug therapy. Feeding a diet specifically designed for senior dogs has been shown to help maintain joint health and mobility.

- Moderate weight loss in overweight senior dogs can significantly reduce lameness due to hip osteoarthritis
- Feeding adequate amounts of high-quality protein can help maintain optimal muscle tone and mass to help maintain healthy mobility
- Optimal ratio of omega-3: omega-6 fatty acids and antioxidants to neutralize the deleterious effects of free radicals, which are thought to be involved in the development of damage to joint tissues, and favorably alter tissue inflammatory mediators
- Chondroprotectives aid in maintenance of healthy cartilage, with increased cartilage synthesis and decreased degradation observed in vitro
- Low-impact exercise can help maintain healthy weight, muscle mass and joint function for dogs with osteoarthritis

THE SCHNAUZER HOUR: IF CONFUSION IS THE FIRST STEP TO KNOWLEDGE, I MUST BE A GENIUS

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KEY POINTS

- Miniature schnauzers are affected by several medical disorders that often exist concurrently in the same patient. Nutritional therapy is a key component of managing miniature schnauzers with many of these disorders. Designing a therapeutic regimen may be challenging because treatment of one condition may be contraindicated or not ideal for the other(s).

It is relatively easy to design a treatment plan for pets with a single diagnosis such as obesity, chronic kidney disease, or atopic dermatitis; however, what would you recommend for the patient that has all three? Miniature schnauzers are a popular breed of dog, ranked in the top 10 breeds in the United States, based on annual registrations in 2005 and 2006 by the American Kennel Club (www.akc.org). Miniature schnauzers are known to be at risk for many medical disorders. It is not uncommon for some dogs to have several of these disorders at the same time, presenting a therapeutic challenge for veterinarians. This article reviews nutritional management of common disorders in miniature schnauzers, with guidelines for managing patients that have multiple disorders concurrently.

NUTRITIONAL MANAGEMENT OF COMMON DISORDERS IN MINIATURE SCHNAUZERS

Anyone who has worked in a small animal hospital is well aware of the classic miniature schnauzer patient with pancreatitis, urolithiasis, diabetes mellitus, and potentially a few other disorders (calcium oxalate uroliths, obesity, hyperlipidemia, etc). Treatment for each disorder will be reviewed initially and then a summary of tips and guidelines will be included for managing patients that have more than one disorder concurrently.

Pancreatitis

The goals of nutritional management of patients with pancreatitis are to decrease stimulation of pancreatic secretions and provide adequate nutrient levels to support recovery. Traditionally it has been recommended to "rest" the pancreas by withholding oral intake during the initial phase of acute pancreatitis; however, this practice has been questioned. Currently it is suggested that oral intake only be restricted in patients with persistent/uncontrollable vomiting and then for as short a time as possible. Long-term management should include feeding foods with relatively less fat and that avoid excessive protein since both are stimuli for pancreatic secretion. A moderate-fat food (10–15%, dry matter basis) is recommended for patients recovering from pancreatitis, whereas a low-fat food (<10%, dry matter basis) is more appropriate for those with concurrent obesity or hypertriglyceridemia. High-fat commercial foods (> 20%, dry matter basis) and human foods should be avoided. Patients should be evaluated periodically to determine effectiveness of treatment and help reinforce importance of nutritional management.

Hyperlipidemia

Hyperlipidemia indicates an abnormal amount of lipids (either cholesterol or triglycerides) in the blood. Postprandial hyperlipidemia may occur for 6 to 12 hours after a meal in normal dogs; however, serum triglycerides should not exceed 500 mg/dL. Concentrations >1000 mg/dL (in fasted or postprandial samples) strongly suggest an underlying disorder of lipid metabolism. Hyperlipidemia most often occurs secondary to metabolic/endocrine disorders (diabetes mellitus, hyperadrenocorticism, and hypothyroidism). Primary hyperlipidemia, characterized by excessive serum triglyceride concentrations, occurs in miniature schnauzers and other breeds. The exact mechanism of primary hyperlipidemia is unknown; it may result from a lack of lipoprotein lipase activity. A recent report revealed that nearly 33% of healthy miniature schnauzers had abnormal serum triglyceride concentrations compared with 5.3% of control dogs. Because of increased risk for pancreatitis in dogs with elevated serum triglyceride concentrations, it may be reasonable to include this measurement in routine wellness examinations of miniature schnauzers.

Feeding a low-fat food should be the initial step in managing patients with primary hypertriglyceridemia. Miniature schnauzers with persistently increased serum triglycerides (> 500 mg/dL) are candidates for dietary intervention whether clinical signs exist or not. While controlled clinical studies have not been performed to determine the ideal amount of dietary fat for these patients, it has been suggested that moderate intake (8–12% of diet, dry matter basis) is often sufficient to control hypertriglyceridemia. This is supported by several published case reports of miniature schnauzers managed successfully with Prescription Diet® r/d® Canine. Effect of nutritional management should be assessed 3 to 4 weeks later and should include the pet owners evaluation of patient response, body weight and condition, and laboratory evaluation of blood collected after a 12-hour fast. Goals of nutritional management are to achieve a clear serum sample and total serum triglyceride concentration <500 mg/dL. An alternative goal for some patients is slight serum turbidity and serum triglycerides < 1000 mg/dL. If these goals are not achieved and the owner is complying with nutritional recommendations (ie, feeding exclusively the low-fat diet and not inappropriate treats or foods), consider additional treatment. Increased supplementation with omega-3 fatty acids may lower triglyceride concentrations although clinical studies to support their use are lacking; doses ranging from 10 to 30 mg/kg to 200 mg/kg orally every 24 hours have been recommended.

Diabetes Mellitus

Increasing fiber content of the food is indicated to manage or prevent obesity and improve glycemic control in dogs with diabetes mellitus. Increased dietary fiber is associated with slowing of intestinal glucose absorption with subsequent improvement of glycemic control. Studies in diabetic dogs have documented glycemic improvement in response to consuming foods with increased amounts of soluble and insoluble fiber. It is recommended that foods for managing diabetic dogs contain 10% to 15% fiber (dry matter basis). Patients should be monitored for side effects including constipation (insoluble fiber), diarrhea and flatulence (soluble fiber), and thin body condition. Gradual transition over a period of 1 to 2 weeks to high-fiber foods may help increase acceptance by some dogs, especially picky eaters. Because of increased risk for obesity, pancreatitis, altered lipid metabolism, and potential for causing insulin resistance, excessive dietary fat should be avoided in diabetic dogs. It has been recommended that dietary fat should be <20% (dry matter basis) and <30% (metabolizable energy basis).

The feeding schedule should be designed to enhance actions of exogenous insulin and minimize postprandial hyperglycemia. In general, dogs receiving insulin twice daily are fed equal-sized meals immediately before each insulin injection. If insulin is only given once daily, half of the daily caloric intake is given at the time of insulin injection and the remainder is fed 8 to 10 hours later. Dogs that prefer to eat multiple, small meals throughout the day should be allowed to continue their eating pattern (as long as it does not contribute to obesity).

Calcium Oxalate Urolithiasis

Feeding moist food or adding water to the food is recommended in all dogs because it appears to decrease risk of calcium oxalate uroliths. There are several commercial foods that are recommended to prevent calcium oxalate uroliths in dogs including Hill's Prescription Diet® u/d® Canine and w/d® Canine and Royal Canin Urinary SO.™ Prescription Diet® u/d® contains potassium citrate (a calcium oxalate inhibitor); Canine w/d® does not, therefore it should be added in patients eating this food. Calcium oxalate stone-forming dogs had decreased urine calcium and oxalate concentrations after being fed Urinary SO™ for 1 month. There were no clinical signs of disease recurrence for 1 year; however, diagnostic imaging was not performed to confirm presence or absence of uroliths.

Additional treatments (eg, thiazide diuretics and/or potassium citrate) should be considered in dogs that have recurrence despite nutritional management. Administration of hydrochlorothiazide (2 mg/kg PO every 12 hours) decreased urinary calcium excretion and urine calcium concentration in dogs with calcium oxalate urolithiasis; the greatest reduction in urine calcium concentration occurred in dogs fed Hill's Prescription Diet® u/d® Canine. compared with hydrochlorothiazide alone. Effectiveness of potassium citrate alone has not been evaluated in dogs with urolithiasis; however, it may be considered in patients with recurrent disease (50–75 mg/kg PO every 12 hours).

Because of the high rate of recurrence, patients should be monitored periodically. This allows for adjustments in treatment, removal of uroliths that may cause urinary obstruction, and evaluation for metabolic disorders (e.g., hyperadrenocorticism, hypercalcemia) that may be associated with calcium oxalate urolithiasis.

GENERAL GUIDELINES FOR MANAGING PATIENTS WITH MULTIPLE DISORDERS

Many patients, especially miniature schnauzers, often have many of the disorders discussed previously as well as others (eg, chronic kidney disease, adverse food reactions, and hyperadrenocorticism). While there are no published studies evaluating different treatment regimens in these complicated patients, below are helpful guidelines to consider.

- Try to determine if one disorder is potentially causing others and treat the primary disorder first. For example, chronic pancreatitis may predispose to chronic kidney disease (glomerulonephritis secondary to chronic inflammation). Trying to prevent recurrences of pancreatitis (by feeding a low-fat food) may take precedence over feeding a therapeutic renal food (which often is higher in fat).
- Identify which disorder has the most potential for affecting quality of life or lifespan and manage it initially.
- If multiple disorders may equally affect quality/quantity of life, try to design a treatment regimen that will help manage all conditions, realizing it may require a compromise of ideal treatment for each individual disorder. For example, if management of chronic kidney disease and pancreatitis are equally important, it may be possible to compromise and feed a food designed for early kidney disease that has a moderate amount of fat.
- Treatment should be individualized after considering all patient and owner factors. For example, if the owner of a dog with chronic kidney disease is likely to have the pet euthanized if another bout of acute pancreatitis occurs, it would be more reasonable to feed a low-fat food than a renal therapeutic food.
- For patients with multiple problems that require conflicting nutritional management, call the pet food company for a nutritional recommendation. They will usually have a wealth of information to share (that may not be on the pet food label or in the company's product guide).
- For some patients, a homemade diet may be appropriate. In these cases seek input from a board-certified clinical nutritionist who can help design a nutritionally balanced maintenance food tailored for that patients' particular needs.

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MANAGING MICROBES FOR WELLNESS

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Probiotics are defined as beneficial bacteria that confer health benefits to the host. Consumption of probiotic supplements may allow beneficial bacteria that survive transit through the gut to colonize the large intestine and favorably alter the microbial balance. The theory behind these products is that probiotics can help re-establish the bacterial balance in the digestive system and lead to better digestive health following disruption of normal function by factors such as stress, infection, or antibiotic therapy. The most important bacteria that enhance health in humans and pets are bifidobacteria and lactobacilli.

The balance between beneficial and pathogenic bacteria is important for the digestive system and immune function. Harmful bacteria may produce toxins causing diarrhea, invasion of the mucosa, and activation of carcinogens. A balanced microbial milieu prevents invasion by pathogens, provides nutrients essential for proper nutrition by their metabolism which aids in the synthesis of B and K vitamins, and strengthens the immune system by interacting with key immunomodulatory cells. Many factors, such as disease, age, stress, diet, and use of antibiotics, can cause an imbalance between beneficial and pathogenic bacteria. These imbalances can result in a wide range of digestive disturbances, including diarrhea, constipation, vomiting, and gas or bloating. Lower levels of bifidobacteria have been specifically linked to digestive problems including irritable bowel syndrome (IBS) and inflammatory bowel disease (IBD) in humans.

MECHANISMS OF ACTION

The mechanisms by which probiotics may protect the host from potentially harmful organisms are not completely understood, but may involve immune-enhancing and anti-inflammatory activities, modifications to intestinal pH, suppression of pathogenic bacteria through production of inhibitory substances, competition with pathogens for nutrients and growth factors and mucosal attachment sites, and production of lactase. Bacteria in the gut influence the number and distribution of cell types in the gut-associated lymphoid tissue and modulate immune response by mechanisms that are not yet fully understood. It is through a combination of these activities that the full range of probiotic benefits is achieved. With increasing research it is becoming clear that there are differences among various probiotic strains with respect to the types of benefits they are capable of providing.

POTENTIAL HEALTH BENEFITS OF PROBIOTICS

The health effects attributed to the use of probiotics in humans are numerous. Clinical trials have investigated the use of probiotics (lactobacilli and bifidobacteria) in various gastrointestinal disorders. Increases in natural resistance to infectious diseases in the gastrointestinal (GI) tract, suppression of traveler's diarrhea, reduction of bloating, and improvements in lactose intolerance, are among the benefits that have been reported. Potential applications of probiotics in humans are being expanded to include benefits beyond GI disorders. Areas of potential benefit include immune function (eg, allergy and infection prevention), skin health and appearance (eg, treatment of atopic dermatitis in infants and anti-aging of skin in adults), oral health, energy, rheumatoid arthritis, and mental health (eg, stress, depression, and autism).

Many of the same mechanisms by which probiotics may improve human health are applicable in animal health. Lactobacilli and bifidobacteria are part of the natural microflora of healthy dogs and cats. Levels of these beneficial bacteria decrease with age in these animals resulting in less tolerance to dietary changes and stress which may lead to stress-induced diarrhea. As with humans, dietary supplementation with probiotics has been documented to provide GI and immune health benefits in pets.

BENEFICIAL EFFECTS OF PROBIOTICS IN HUMANS

Probiotics are now being evaluated to determine their effects on a variety of human conditions, with a focus on those that have an inflammatory component, including gastrointestinal conditions such as IBS and allergic disorders. Studies have also examined their potential for improving skin health. The role of probiotic organisms in the maintenance of human health continues to be an area of active clinical research.

BENEFICIAL EFFECTS OF PROBIOTICS IN ANIMALS

Given the observed benefits of probiotics in humans, it is reasonable to consider whether similar benefits might be seen in companion animals. Like humans, dogs and cats have short digestive tracts and a complex gastrointestinal bacterial ecosystem. In addition, gastrointestinal tract disorders and skin complaints, in particular, are common in pets, especially when they are under stress. New research is demonstrating that, as in humans, probiotics can positively affect gastrointestinal conditions and skin function in dogs, and is only beginning to define the possible uses of probiotics in maintenance of animal health.

The microbial inhabitants of the GI tract are recognized to have a substantial role in the health of humans and animals. Although it has been known for some time that the microbial flora of the gut are important in the maintenance of GI health and that imbalances in the flora could cause GI disease, it is now recognized that the effects of these organisms extend well beyond the GI tract. Many of the extra-gastrointestinal effects appear to be related to changes in the immune system. Dietary supplementation with probiotic organisms has the potential to provide health benefits to humans and animals with a wide range of conditions, and research will continue to further define the optimal uses of these organisms.

PROBIOTICS IN VETERINARY PRACTICE

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Probiotics are defined as "'live microorganisms which when administered in adequate amounts confer a health benefit on the host." Ideally, probiotics administered to clinical patients should originate in the species being treated and should be nonpathogenic, resistant to digestion by gastric acid and intestinal enzymes, able to adhere to the intestinal epithelium, and capable of influencing host immune responses.

Each organism strain appears to be associated with specific effects on other organisms and on the host, and specific cytokine profiles and biologic effects result from these interactions. Gut bacteria have co-evolved with their host and have become highly specialized over time. Composition of fecal microbiota in individual people is unique but stable over time. Each host has a unique genetic platform (which expresses disease uniquely) and a unique mixture of indigenous flora that can be considered a fingerprint for that host.

SPECIFIC PROBIOTIC EFFECTS ON HOSTS

Effect on Host Nutritional Status

Lactobacilli synthesize B vitamins (niacin, pantothenic acid, pyridoxine, biotin, folic acid) and certain lipolytic and proteolytic digestive enzymes, improving digestibility of food components. Lactobacilli and other enterobacteria also synthesize folate coenzymes that are similar to dietary folate. Microbial fermentation contributes about 7% of maintenance energy in the dog.

Direct Microbial Interactions

A self-regulating population of gut bacteria is maintained through competition, amensalism (symbiotic relationship where one organism is unaffected while the other is negatively affected by its presence), parasitism, and predation. Specific mechanisms of interaction with other microbes include production of antimicrobial factors, competition for adhesion, production of antitoxins such as bacteriocin, and a decrease in lumen pH.

Effects on the Immune System

The gastrointestinal tract is the largest immune organ of the body. Germ free animals display sparse, inactive immune tissues. The immune system recognizes probiotic species types, through microbial pattern recognition or toll-like receptors), leading to specific signal transduction. Activation of these receptors drives nonspecific and specific immune responses. Probiotics also stimulate cytokine responses that lead to proliferation of either TH1 or TH2-like responses, and modifying immunologic tolerance and responsivity

Physical Effects on the Gut

Probiotics may affect the epithelial barrier as well as production of mucus. They may:

- Increase brush border membrane enzyme activity
- Promote epithelial restitution
- Prevent epithelial apoptosis
- Protect tight junctions during inflammation, reducing permeability
- Suppress electrolyte secretion that occurs as part of the pathophysiology of enteropathogen infection
- Increase expression of mucin glycoproteins
- Provide enzymes that may enhance host digestion of ingested nutrients
- Shorten GI transit time

ROLE OF PREBIOTICS

Prebiotics are short- or long- chain polysaccharides which are fermented in the colon for production of energy and carbon, and would not otherwise be absorbed. They reduce pH in the colon because of production of short chain fatty acids (SCFA) as a byproduct of the fermentation process, which also produces H_2/CO_2 gas. Prebiotics appear to increase bifidobacteria counts. Effects of SCFA include:

- Increase sodium absorption
- Energy salvage
- Increase mucosal blood flow
- Regulate cellular proliferation
- Influence cell differentiation and carcinogenesis
- Immune modulation
- Decrease blood cholesterol

Diets high in protein and fat support the growth of *Bacteroides* spp, peptidococci, and Clostridia, while a carbohydrate-rich diet supports the growth of *Bifidobacteria, Lactobacilli, Eubacteria,* and yeasts. Several investigators have found that dogs eating dry, grain-based diets have better fecal bacterial profiles (fewer clostridial and more lactic acid–producing organisms) lower fecal pH with higher short chain fatty acid concentrations, lower bacterial enzyme activity, and lower concentrations of the putrefactive compounds ammonia, sulfide, and indole. Canned, and by inference, grainless 'raw' diets may not support optimal growth of beneficial gut bacteria.

Role in Disease

Many disease states have now been associated with altered gut microbiota, both as a pre-disease condition and as a co-morbid condition. In people, probiotics have good support for the treatment of pouchitis and ulcerative colitis, inflammatory bowel disease, antibiotic-associated and nosocomial diarrhea, and infectious diarrhea. There is encouraging preliminary evidence to suggest that certain probiotics may help prevent the development of allergies in susceptible children, improve immune function, and may help prevent recurrent urinary tract infections. Research is underway to determine whether some probiotics prevent bladder cancer, prevent formation of calcium oxalate uroliths, pancreatitis, and pharyngotonsillitis.

CLINICAL INDICATIONS

Optimizing Performance in Feed Animals

Probiotics have been studied for their ability to improve feed efficiency in food animals for decades, with promising results.

Optimizing Athletic Performance

Art et al administered a commercial yeast-based probiotic to horses in training, and concluded from measurements of respiratory function during treadmill tests that some aerobic metabolic capacities for carbohydrate utilization improved. The effect was noted only during training and not during periods of physical inactivity.

Inflammatory Bowel Disease

In diarrheal diseases, the putative mechanisms of benefit include production of antimicrobial substances including hydrogen peroxide and acids; competition for nutrients; competitive inhibition of receptor binding; antitoxin activity, and immune stimulation.

Endoscopic biopsies taken from 12 dogs with chronic enteropathy were cultured with individual probiotics of canine origin (*L. acidophilus* NCC2628, *L. acidophilus* NCC2766, and *L. johnsonii* NCC2767), a combination of the same probiotic organisms, or placebo. Dogs with enteropathy present for 11 +/- 3 months were diagnosed in a secondary veterinary medical center, and scored using the Canine Inflammatory Bowel Disease Activity Index (CIBDAI). Individual probiotic strains had no significant effect on cytokine levels; however, the combination did lead to changes in proportions of regulatory and pro-inflammatory cytokines. IL10 protein levels increased significantly in samples from sick dogs after addition of the probiotic combination.

Sauter et al collected fecal and endoscopic biopsy samples from 21 client-owned dogs with food-responsive diarrhea. Dogs were supplemented with a probiotic cocktail of *Lactobacillus acidophilus* NCC2628, L. *acidophilus* NCC2766, and *L. johnsonii* NCC2767, and duodenal cytokines and gut microbial populations examined. All dogs improved clinically after probiotic treatment and numbers of Lactobacilli increased, but investigators were unable to associate specific cytokine changes with clinical responses.

Diarrhea

One potential benefit from probiotic treatment of diarrhea is to decrease infection by *C. difficile*, *Salmonella*, and *Campylobacter*. Studies in a multitude of domestic animal species suggest that probiotics can reduce shedding of enteropathogenic bacteria, possibly reducing signs and duration of diarrhea. Unpublished studies by researchers at Nestle Purina (in company literature) have shown that chronic diarrhea in adult cats and kittens may be improved by supplementation with *E. faecium* SF68.

Vahjen examined the effects of *Enterococcus faecium* NCIB 10415 (Enteroferm®) on numbers of fecal *Salmonella*, *Campylobacter*, and *Clostridium* species in 12 client-owned dogs. The daily dose was 9.2 x 10^9 CFU, administered for 18 days, regardless of the dog's size. Dogs in this study experienced a nonsignificant increase in *Salmonella* and *Campylobacter* species if supplemented with Enterococcus (individually, counts on some dogs went up while others went down), but Clostridia numbers were significantly decreased. This strain had been shown in piglets to decrease the pathogenic effects of *E. coli* with no effect on fecal *E. coli* counts.

Results of supplementation of horses at risk for diarrhea and Salmonella infection have been mixed. Commercial probiotic products have been administered to horses that were at risk for development of Salmonella-associated diarrhea. No benefit was noted from supplementation in two studies. Ward found that probiotic supplementation reduced fecal shedding of Salmonella, and suggested that early supplementation, when stress was anticipated, may be effective in reducing Salmonella outbreaks. *Saccharomyces boulardii* (25–50 g PO) significantly decreased severity and duration of signs of acute enterocolitis in hospitalized horses compared with those given placebo. On the other hand, *Lactobacillus pentosus* WE7 actually worsened neonatal diarrhea when given to foals. A trial using different species, *Lactobacillus salivarius* YIT 0479, *L. reuteri* YIT 0480, *L. crispatus* YIT 0481, *L. johnsonii* YIT 0482 and *L. equi* YIT 0483, found that supplementation enhanced growth and decreased diarrhea in foals.

General Immune Function

Studies using different organisms in a variety of laboratory animals, as well as in people, suggest that many probiotic species can influence immune function. Administration of *Enterococcus faecium* SF68 (5 x 10^8 CFU daily), when administered to puppies from weaning to 1 year of age, had effects on immune function. Total fecal IgA levels tended to be higher in the group treated with probiotic in their diet as compared with those given diet alone ($P = 0.056$). Plasma IgA was higher in the treated group, where plasma IgG did not differ between the groups. Response to distemper vaccination (measured by CDV-specific IgG and IgA) was stronger in the treatment group ($P < 0.05$). There was also a greater proportion of mature B cells in puppies fed the probiotic. The investigators showed that these effects were due to immune modulation by SF68, as opposed to changes that were due to manipulation of the bacterial population (Benyacoub, 2003). *E. faecium* SF68 was also shown to increase fecal Lactobacilli and reduce *C. perfringens* and *E. coli* in treated animals.

Allergies

The relationship of gut bacteria and immune-mediated diseases is the subject of much recent research. In humans, it is well established that the prevalence of autoimmune diseases and allergy has risen dramatically. The hygiene hypothesis asserts that reduced exposure to infectious organisms during childhood predisposes people to allergic and immune-mediated diseases later in life. This reduced exposure is thought to occur because of antibiotic use, environmental antiseptics, increased food safety, and other strategies to "keep clean." Probiotics may have a potential role in replacing some of these commensal bacteria. Whether probiotics have utility in the treatment of canine atopic dermatitis is unknown, but interesting human clinical trials suggest that they may be considered in the prevention of atopy in at-risk individuals. Caution should be used when considering probiotic use in sick young animals, because oral administration of antigens with invasive microbes results in immunity, rather than tolerance.

Recurrent Urinary Tract Infections

Preliminary studies in women indicate that probiotics could be considered for dogs and cats with chronic recurrent urinary tract infections, after common causes such as hyperadrenocorticism have been ruled out.

Chronic Renal Disease

Uremic toxins diffuse passively from the blood into the gut lumen. Urease-producing probiotic species hydrolyze urea and maintain a concentration gradient that favors more diffusion of urea from blood to gut lumen. Experimental animal studies in pigs using the patented product Azodyl (a combination of *Enterococcus thermophilus, Lactobacillus acidophilus,* and *Bifidobacterium longum*) showed that supplementation reduces uremia and death. A case series in seven azotemic cats was reported from a clinical practice. After 60 days of administration, all cats experienced a decrease in BUN and six of seven cats showed a decrease in creatinine. Concurrent treatments varied among the cats and previous history was not reported. Only one cat appeared to receive probiotic therapy alone, eating commercial cat food and receiving no fluids. While the creatinine was reduced from 2.6 to 2.2, the cat lost weight (0.5 lb). Provided dogs and cats with CRD are not severely immunocompromised, preliminary studies suggest a potential use for probiotics in this condition.

Pancreatitis

Gut bacterial translocation during pancreatitis can lead to septicemia and worsens patient prognosis significantly. Some studies using *Lactobacillus plantarum* 299 have suggested that high doses of lactic acid-producing bacteria can suppress inflammation that makes SIRS (systemic inflammation response syndrome) such a deadly event in acute pancreatitis.

Investigators have studied dogs with experimental severe pancreatitis, providing either parenteral nutrition, elemental enteral nutrition, or supplementation with probiotics. In this study, serum amylase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), plasma endotoxin, pancreatic and ileal histopathologic changes, and the degree of bacterial translocation were significantly decreased with probiotic treatment. An earlier study documented similar results.

Safety

A 2004 review found 23 probiotic species of *Lactobacillus* involved in 89 severely ill patients with lactobacillus bacteremia. Predisposing factors were immunosuppression, prior prolonged hospitalization, and prior surgical interventions. *Lactobacillus rhamnosus* GG has been associated with bacteremia after administration to a child with short gut syndrome. It has also been suggested that *Lactobacillus* spp. produce organic acids that may lead to decalcification of dental matrix.

There have been a number of reports (92 cases as of 2005) of invasive infection by *Saccharomyces boulardii*, a subspecies of *S. cerevisiae*, usually when it was administered to patients with diarrhea. Intravascular catheter placement and antibiotic therapy were common features in these patients. Septicemia due to ingestion of a probiotic strain of *B. subtilis* was reported in a 73-year-old leukemia patient.

Septicemia with probiotic organisms following supplementation has not been reported in companion animals to this author's knowledge. Caution is advised if supplementation is considered in immunosuppressed or severely ill animals, or in those where marked compromise of the intestinal mucosa is suspected.

Quality Control

Studies indicate that commercial probiotic products are subject to large variations in quality control. Problems may range from viability issues to inclusion of species not listed on the label.

Health food store brands in Canada commonly contained (in addition to the organism on the label) a strain of lactobacillus not listed on the label. More recently, a ConsumerLab.com analysis of over the counter brands of probiotic found that of 13 human products sampled, four did not contain the amount listed on the label; four did not contain the generally accepted effective dose of 10^9 organisms; and none of the human products were found to have microbial contamination. Of three animal over-the-counter products tested, one did not contain the amount claimed on the label, two did not contain the recommended 10^9 per daily dose, and one was contaminated with mold.

Weese analyzed over-the-counter 23 animal probiotic products and 21 human products for their adherence to label claims. Bacterial species were misspelled (in up to 25% of products) and species were frequently misidentified (either by using outdated names or by naming a nonexistent organism). Based on the deficiencies found by Weese, practitioners and consumers should expect to see the following on a probiotic product label: all organisms included down to the strain level; correct spelling and identification of all organisms in the product, and the number of live organisms expected on the expiration date. A more recent study of five products on the European market yielded similar results.

"Holistic" dog and cat commercial diets sometimes list probiotics in their ingredients. Thirteen commercial diets for dogs, and six commercial diets for cats, all claiming to contain probiotics, were analyzed for their content of species listed on the labels. Twelve diets did not list a live organism (consistent with the claim to contain a probiotic) but rather probiotic fermentation products. Only 53% of the diets contained at least one of the listed species and none contained all of the probiotics listed on their labels

Investigators at Waltham added *L. acidophilus* to dog food, and got 71% recovery before the study started, and 63% recovery 8 weeks later. The investigators processed the food for minimal moisture content (2%), stored it in aluminum bags, gave the food to the dogs in dry form without water, and minimized exposure to moisture while it was presented to the dogs, thus maximizing the dose.

There is some debate on the value of nonviable probiotic bacteria. Most recent clinical studies suggest that nonviable organisms do not have probiotic effects. Nonviable bacteria and bacterial DNA components (from VSL#3), and probiotic cultured media have had beneficial effects in induced colitis models and in knockout mice predisposed to colitis. On the other hand, one study using heat inactivated *L. rhamnosus* GG was terminated prematurely due to adverse gastrointestinal effects.

References are available from the author upon request.

NUTRACEUTICALS IN CLINICAL PRACTICE

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A *nutraceutical* is defined by the American Dietetic Association (ADA) as any non-toxic food component that has scientifically proven health benefits, including disease treatment or prevention, although many other definitions have been advanced. The North American Veterinary Nutraceutical Council defines a nutraceutical as “a substance which is produced in a purified or extracted form and administered orally to patients to provide agents required for normal body structure and function and administered with the intent of improving the health and well being of animals.” Herbs are not considered nutraceuticals. The following are nutraceuticals I consider to be very useful in general veterinary practice.

ANTIOXIDANTS

An antioxidant is any substance, which when present in low concentrations compared with those of an oxidizable substrate, significantly delays or prevents oxidation of that substrate (Halliwell, 2002).

Cellular metabolism normally leads to the production of free radicals (or reactive oxygen species or ROS). There are a variety of free radicals, usually existing in a state with an unpaired electron, which makes it a reducing *or* an oxidizing agent depending upon the molecule and the milieu. Oxygen free radicals may be the most biologically important. Hydroxyl radicals are particularly damaging, and are formed in close proximity to mitochondrial membranes, so they represent a special threat to them. *Oxidative damage* has a physiologic function in helping to suppress the growth of bacteria and other pathogens, so antioxidants should not be used inappropriately. *Oxidative stress* is viewed as a relative overproduction of oxidizing or reactive materials that overcome the detoxification pathways.

Certain vitamins, minerals, enzymes, carotenoids, and other substances such as flavonoids and melatonin have antioxidant activity. Endogenous or dietary antioxidants control damage that might be induced by these ROS by scavenging them, regulating cell–cell communication, second messenger pathways, or regulating apoptosis or inflammatory events. When ROS activity exceeds the antioxidant potential, damage may occur to cell lipids, protein and DNA. Whether exogenous supplementation of antioxidants above currently recommended levels may control this damage and thereby influence the course of various diseases is an active area of research.

Animal and human clinic al studies suggest that certain antioxidants may reduce liver damage and fibrosis (vitamin E, milk thistle flavonolignans, SAMe), reverse or improve the signs of cognitive dysfunction (vitamin E, C), improve respiratory function in human chronic obstructive pulmonary disease (COPD) and congestive heart failure (CHF) patients (flavonoids, superoxide dismutase, CoQ10), improving immune function in humans and laboratory animals (vitamin E), improve signs of osteoarthritis in dogs and people (vitamin C), and decrease exercise-induced oxidative stress in humans. Whether antioxidants can help prevent immune suppression due to hard exercise in horses is an active field of research.

Antioxidants may slow proliferation of neoplastic cells and reduce adverse effects of chemotherapy. While many believe that antioxidants interfere with chemotherapy, others suggest that they actually enhance the effects of chemotherapy (Conklin, 2000). Cancer itself causes oxidative stress in the host. Chemotherapy also imparts oxidative stress to the organism, however, only certain drugs exert their effect on cancer cells specifically through oxidative stress mechanisms (mitomycin C, bleomycin, and possibly anthracyclines such as doxorubicin). One author (Conklin, 2004) opines that the oxidative stress caused by tumor and chemotherapy actually generates toxic aldehydes that slow cell cycling, allowing tumors to repair DNA or go into cell cycle arrest until chemotherapy is discontinued. Using this reasoning, he suggests that antioxidants will enhance tumor cell killing. However, not all antioxidants are the same and it is important to define which ones are effective and safe for each chemotherapeutic agent.

Some trials suggest that antioxidants are effective in mitigating the side effects of chemotherapy and radiation, and improve quality of life. Human clinical trials addressing this subject have been published, but the evidence is still conflicting (Block, 2004). A critical review of 50 randomized controlled trials or observational studies reporting concomitant use of nutritional supplement and chemotherapy and/or radiation therapy was recently published. In 15 of those studies, 3738 patients out of a total of over 5000 took antioxidants and other nutrients, and were reported to have increased survival (Simone, 2006).

There is increasing evidence that high doses of antioxidants can cause harm (Bjelakovic, 2007a), (Lawson, 2007). High doses may have pro-oxidant activity, and animal studies have shown that vitamin E interferes with the benefits of fish oil or chemotherapy in cancer patients. Bjelakovic (2007b) opines that one possible mechanism for these poor outcomes is that generation of free radicals is an essential process for control of unwanted cells and pathogens, and if prevented, may subject the organisms to greater risks of cancer and other conditions

Because some antioxidants may work via specific binding proteins, it is thought that certain antioxidants may target specific organs or conditions more efficiently. Antioxidant combinations take advantage of the fact that many antioxidants work synergistically, or in some cases, require each other's presence for proper function. These combinations typically contain vitamin A (or beta-carotene, or both), vitamin C, vitamin E, alpha-lipoic acid, mixed carotenoids, mixed flavonoids, and selenium.

I use combination antioxidants primarily in geriatric animals, where they may slow progression of cognitive dysfunction and osteoarthritis. These combinations usually contain vitamin A, E, C, selenium, flavonoids, and CoQ10. If started late, clients and clinicians may actually observe partial reversals in these diseases. Specific antioxidants are appropriate in other conditions: white tea for radiation mucositis, silymarin/SAMe/vitamin E/zinc for liver diseases, and combinations for cancer and chronic inflammatory diseases.

Alpha-lipoic acid is toxic to cats as compared with dogs or humans, and doses above 13 mg/kg may result in hepatotoxicty, anorexia, hypersalivation, ataxia, hyper-irritabiltiy and perhaps chronic accumulation with eventual toxicity at lower doses.

FATTY ACIDS

Fatty acids are named for the number of carbons they contain, and the position of the first double bond in relation to the methyl end of the carbon chain. Animals can manufacture, desaturate and elongate fatty acids endogenously, but cannot alter the placement of the double bonds.

Fatty acids are components of the cell membrane, and diet intake directly influences the phospholipids composition of the cell membrane. n-3 fatty acids have a number of effects in cells, influencing membrane fluidity, permeability, and lipid packing; the activity of proteins such as protein kinase C and Na+ K+ ATPase; gene synthesis, and eicosanoid synthesis (Siddiqui, 2004). They may also modulate matrix metalloproteinase activity (Roudebush, 2005). n-3 and n-6 fatty acids compete for the enzymes that elongate and desaturate these compounds. When the cell membrane is damaged, membrane phospholipases react with these enzymes and the fatty acids are incorporated into leukotrienes and prostaglandins. n-6 fatty acids are incorporated into the more inflammatory PGE2 and LTB4, while n-3 fatty acids are incorporated into the less inflammatory PGE3 and LTB5.

ALA, EPA, and DHA are omega-3 fatty acids with some support for use in dogs. An anti-inflammatory omega-6 fatty acid is GLA, but other omega-6 fatty acids are generally considered pro-inflammatory. ALA is converted inefficiently to DHA. EPA can be converted at a 23% rate. When ALA is the main dietary omega-3 fatty acid, DHA does not accumulate in nerve tissue, which contrasts to the situation when DHA or EPA are supplemented. Black currant seed oil is 17% GLA and 13% ALA. Evening primrose oil contains 8–10% GLA, while borage oil contains at least 23% GLA. Flax seed oil contains about 55% ALA and 15% LA.

The relative ratio of anti-inflammatory and pro-inflammatory fatty acids ingested will influence the course of inflammatory diseases. For instance, dogs eating defined diets high n-3 fatty acid may be less likely to respond to additional supplementation. In dog foods sold in Norway, the omega-6:3 ratio varied from 5:1 to 17:1 (Ahlstrom, 2004). Disease or genetics-associated differences may suggest that an alternate strategy is to try different fatty acids for supplementation, such as an anti-inflammatory n-6 fatty acid (GLA) if dogs are already eating defined diets.

Some have suggested that it is the absolute amount of ingested omega-3 fatty acid that matters (Watson, 1998; Mazaffarian, 2005; Hwang, 1997). Decreasing n-6 fatty acid consumption does not produce the same benefits as those of increasing n-3 consumption, however (Ahlstrom, 2004). One commercial pet food company, on the other hand, promotes the idea that the total daily omega-6:3 ratio is the most important determinant of overall response to treatment and there are papers that support that (Khor, 2004). Enzymes that desaturate fatty acids have a higher affinity for omega-3 fatty acids (Holman, 1998; Moore, 1990), and the recommendation for at least a 15:1 n-6:n-3 ratio was developed from this established enzyme affinity; however, this theory has not been evaluated in vivo.

Effects of polyunsaturated fatty acids in companion animals have been studied most in the treatment of atopy, immune responses, lipid metabolism, platelet activity, and more recently cognitive development. Studies and clinical use suggest that only some animals will respond to treatment with fatty acids. Some have suggested that the differences in response reflect differences in plasma triglyceride clearance, delta 6 desaturase deficiency or delta-5-desaturase deficiency (Abba, 2005).

Clinical Effects

Omega-3 fatty acids were not considered essential until recently because they are less efficient in resolving signs of fatty acid deficiency (impaired growth, dermatitis) compared linoleic and arachidonic acids. DHA is now considered to be essential for normal development and maintenance of the nervous system.

Evidence from in vitro and laboratory animal studies suggest that EPA and DHA from fish oil have anticancer effects, and human epidemiologic studies tend to suggest the same. Eicosanoid generation, controlled in part by COX-2, may be involved with the development and progress of a number of tumors. DHA is an n-3 fatty acid, which is a component of fish oil, and may down-regulate expression of COX-2 (Tapiero, 2002). EPA reduces protein catabolism and lipolysis, and so helps to prevent cancer cachexia (Roudebush, 2005).Clinical trials in dogs with lymphoma, nasal tumors, hemangiosarcoma, and osteosarcoma also support the use of fish oil in companion animals with cancer. Clinical studies of fish oil use in dogs with cancer are claimed to prove that fish oil is beneficial; however, these studies are complicated by the use of other strategies, such as arginine supplementation and a low carbohydrate diet. However, feeding the diet high in fish oil did result in higher serum levels of EPA and DHA, and survival was improved in these dogs (Roudebush, 2005).

Approximately 20% of canine atopic patients can be controlled with fatty acids (usually omega-3) alone, but the effect can take up to 12 weeks to develop (Saevik, 2004). Fatty acids can reduce the need for corticosteroids and antihistamines in up to 100% of atopic dogs (Scott, 1997). Black currant seed oil given to dogs at 100 mg/kg/day reduced pruritus in 70% of the dogs treated (Noli, 2006). In another trial, 61.5% of dogs treated with the same dose of black currant seed oil experienced some degree of benefit. Two of thirteen dogs did not develop their usual atopic signs at all while treated (Toma, 2006). Evening primrose provided clinical benefit to atopic dogs (Scarff, 1992), and other trials using EPO in combination with other fatty acid supplements suggest a benefit in cats (Harvey, 1993a). (Harvey, 1993b). Reviews of use of evening primrose oil in human atopy suggest that while results are mixed, there is a definite benefit for 10–20% of patients, over and above placebo (Hoare, 2000). Flax oil (Mueller 2004) and EPA + DHA from fish oil (Abba 2005, Logas, 1994) have shown benefit for atopic dogs.

Dose

The dose of fish oil suggested by the studies of lymphoma in dogs is equivalent to 360–600 mg/kg BW of the combination of EPA and DHA in fish oil. This can be achieved (expensively) by using fish oil as the fat source in a homemade diet. Most pet owners who are unable to feed N/D find supplementing the diet with a lower dose to be acceptable, though it is unknown if these low doses are effective. For this purpose, I recommend a dose of 120–240 mg/kg BW, which is 1–2 extra strength capsules per 5 kg BW.

Cats do not possess the enzyme responsible (delta-6-desaturase) for conversion of ALA to EPA or DHA, although an alternate pathway through delta 5 and delta 8 desaturases may exist (Bauer, 2006). In people and dogs, and even in the latter two species, conversion is considered inefficient. Long chain PUFAs may therefore be conditionally essential in cats. Dogs are said to convert ALA to DHA with about 6% to 10% efficiency. Most researchers believe that any effect ALA has as on anti-inflammatory and immune modulatory activities are due to its conversion to DHA.

Safety

Older studies on the effects of fatty acid supplementation for 4 or 6 weeks on bleeding time in dogs were contradictory (Casali, 1986; Landhmore, 1986) Boudreaux (1997) examined platelet reactivity when beagles were fed n-6:n-3 diets with ratios ranging from 5:1 to 100:1 for 12 weeks. Platelet aggregation, serotonin release, fibrinogen concentration and anti-thrombin III activity were not effected by changing fatty acid ratios. Saker (1998) found that when cats were fed n-3 enriched diets for 112 days, bleeding time was increased, and platelet activation and aggregation was lower, although APTT and OSPT were not affected. Very high levels (100 g/day) have led to increased liver enzymes (ALT, AST) in humans. Increasing the total daily omega-3 intake increases the requirement for Vitamin E (0.4 mg of alpha-tocopherol to 1 g PUFA) and perhaps other nutrients required in fat metabolism

GLUTAMINE

Glutamine is conditionally essential, and plasma and muscle levels are decreased in animals with tumors. Studies have suggested that it can stabilize weight, improve gut barrier, improve immune function, and enhance the effects of chemotherapy and radiation. Glutamine is contained in cabbage, beets, beef, chicken, fish, beans, and dairy products, and even if these items are included in a pet food, the glutamine concentration is not likely to be listed. If a low-protein food is being used (commercial or homemade), glutamine supplementation may make sense. It may also be indicated for animals with gastrointestinal adverse effects from chemotherapy, weight loss, and low lymphocyte counts. The usual dose is 500 mg/kg divided daily.

PROBIOTICS AND FRUCTO-OLIGOSACCHARIDES

Probiotics are living organisms taken orally to influence the ecology and function of the gut. Current best evidence in humans suggests that they are effective in the treatment of antibiotic-associated diarrhea, infectious diarrhea, and inflammatory bowel disease. There is emerging evidence that proper gut ecology is important in the 'immune education' process, and that probiotic supplementation especially in the young may help to reduce the incidence of atopy.

Probiotics may work via competitive inhibition of enteropathogens, production of substances that suppress the growth of other bacterial species, through stimulation of anti-inflammatory cytokine production and by immunemodulation in the gut (which also has systemic immune effects). Various *Lactobacillus, Bifidobacteria, Enterococcus, Saccharomyces*, and *Bacillus* species have been used in clinical trials ranging from growth enhancement and disease prevention in food animals to performance enhancement in horses.

Different species may have different clinical effects, and the potential for pathogenic effects (especially with *Enterococcus* species) exists. In human medicine, one of the most promising products is Lactobacillus Strain GG. Multiple independent analyses have shown that quality control issues abound among this class of nutraceuticals; products very frequently contain either fewer viable organisms than promised on the label or in some cases, different organisms than labeled. On the other hand, some studies suggest that live organisms are not necessary for some of the beneficial effects.

Weese et al determined that in pet foods containing probiotics, none of the tested products contained viable organisms. In another study, none of the veterinary probiotic supplements tested were accurately labeled. Quality control is a major determinant of efficacy and most products do not meet quality standards. VSL#3 and Culturelle (both human products) are the best investigated products.

I use probiotics for any chronic diarrhea, chronic antibiotic use, food allergy, inflammatory bowel disease, and in some cases of immune suppression. Probiotics are in general are very safe, although a few cases of septicemia with probiotic species have been reported in gravely ill humans. I use human doses down to 10 lbs, and then divide that by half.

References available from the author upon request.

ADVERSE FOOD REACTIONS: UNDERDIAGNOSED?

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Many veterinarians believe food allergy to be uncommon in dogs and cats. While food allergy is the third most common allergy seen (behind atopy and flea allergy), it still accounts for 10% of all allergic skin disease. The most recent critical review of the evidence suggests that 17.4% of dogs undergoing an elimination diet trial had food allergies. The diagnosis of food allergy is not easy, for veterinarians or pet owners, and it is possible that these numbers underestimate the prevalence of this disease.

True allergy to food ingredients must be distinguished from food intolerance. Food allergy is an IgE-mediated hypersensitivity to food proteins ranging from 10 to 70 kDa in molecular weight. Reactions may follow inhalation, ingestion or skin contact, and usually occur within 2 hours of contact, and are reproducible.

PATHOPHYSIOLOGY OF THE ALLERGIC RESPONSE

The gut is contiguous with the external environment and has evolved special mechanisms that allow the body to absorb ingested nutrients while protecting it from potentially harmful pathogens and toxins. Sources of allergenic proteins and glycoproteins include those in meats and grains (primarily), bacteria, and self antigens from sloughed cells, secreted enzymes and immunoglobulins. Protection from allergens in the gut occurs at the intestinal mucosal level (which includes protection due to peristalsis, the mucous layer, the breakdown of food antigens through digestive enzymes, etc); at the gut-associated lymphoid tissue (GALT), which samples/recognizes antigens, and binds them for absorption and/or destruction), and at the hepatosplenic macrophages, by removing immune complexes).

When the gut mucosal barrier is breached, sensitization to proteins—food, microbial, and self—may or may not occur. Proteins and glycoproteins are absorbed continuously, and the immune system differentiates between self and non-self (or dangerous and not dangerous) antigens constantly, based on development of tolerance. Tolerance is a specific immunologic reaction; it is based not on general nonresponsiveness, which would deprive the animal of defense against pathogens, but on selective nonreactivity to certain antigens. This development should logically occur at weaning when new foods are introduced, but the exact timing is unknown. Dermatologists and allergists tend to recommend limiting antigenic exposure early in life, especially because viral infections during development can breach gut mucosal defenses, but a recent study suggests that in dogs, oral tolerization to specific antigens can occur with early exposure.

When antigens escape from the gut and liver and reach general circulation, they may stimulate sensitized basophils or IgE bearing mast cells causing reactions in skin and ears. In people, delayed type hypersensitivity reactions may also be seen as recurrent abdominal pain, fatigue. The rate of sensitization can be very rapid in some animals and people. In people, a rotational diet strategy has been developed based on the finding that some people become sensitized to elements in their diets in as little as 4 days.

Verlinden (2006) states that sensitization occurs slowly and that food allergic patients will have been fed the offending food for at least 2 years, though acknowledging that some young animals less than one year may be affected. Many animals can be fed the same novel or hydrolyzed protein diet for life, but if signs recur, sensitization to the dietary proteins should be considered. In animals, having a 'stable' of three to four different diets allows a rotation of 7 days, with at least 14 days between reintroduction of any single diet. Most animals are not sensitive enough to require a rotation this frequent—changing every 4 to 8 weeks is often sufficient. However, a common reason for missing a diagnosis of food allergy is neglect of those animals who become sensitized within days of introduction to a new diet!

HISTORY AND CLINICAL SIGNS

Food allergy is more common in boxers, cocker spaniels, springer spaniels, collies, Dalmatians, German shepherd dogs, Lhasa apsos, miniature schnauzers, retrievers, shar-peis, soft coated wheaten terriers, dachshunds, and West Highland White terriers. In cats, GI signs may be more common and Siamese and Birman cats may be more at risk. Between 33% and 51% of patients show signs of food allergy before one year of age. In people, food allergies are most common in the young, including infants.

Recent changes in diet may or may not be found in the history, since sensitization may occur over days to years. Most pets eat commercial foods containing combinations of allergens, so pets are constantly exposed to greater or lesser levels of allergens, even as they change diet brands. Signs that cycle over time are not uncommon.

In dogs, nonseasonal pruritus, especially on face, paws, trunk, axillae, inguinal and perineal areas, and ears, is common. In cats, military dermatitis often around head, neck and ears, and chronic otitis are common, and eosinophilic granuloma complex may also be related in some cases. Corticosteroid therapy may or may not lead to relief. Vomiting and (especially in dogs) diarrhea can be seen, but there is disagreement over how often GI and skin signs are seen together; some authors claim the association is rare while one dermatologist sees the association up to 60% of the time. Food allergy is implicated in some cases of inflammatory bowel disease. Protein losing enteropathy in wheaten terriers and gluten enteropathy may sometimes respond to food antigen manipulation.

Other signs of food allergy could include rhinitis and asthma. This is well recognized in people but rarely published or discussed in veterinary medicine as yet. Seizures have also been implicated as a sign of food allergy, but there is only one report in older literature about a possible case.

ELIMINATION DIETS AND FOOD CHALLENGE

Food elimination and challenge are the only accurate diagnostic tests for food allergy; serum IgE and skin testing are not recommended. In early studies, the most common allergens in dogs in Germany as detected by scratch test were (in descending order), cereals and meat (in equal numbers), egg, milk and fruit, vegetables, chocolate, beef and pork. The majority of dogs were less than 1.5 years of age when signs occurred. A recent review of seven studies indicates that dogs are most commonly allergic to the following foods (in descending order): beef, dairy, wheat, egg, chicken, lamb/mutton, soy, pork, rabbit and fish. In cats, the most common allergens are beef, dairy, fish, lamb, poultry and barley/wheat (in equal numbers), egg and rabbit in equal numbers. Note that vegetables and fruits were not evaluated. Most animals are allergic to more than one antigen.

Characteristics of elimination diets should include: no previous exposure to the proteins in the diet, a simple formula with as few proteins as possible, a low protein level, no vasoactive amines or additives, and nutritionally adequate. A low protein content may lower the allergic threshold by reducing proteins that go into forming immune complexes, but is primarily directed toward reducing the potential for nonimmunologic reactions.

The allergenicity of an individual protein may change when it is processed, because cooking can expose new epitopes as the protein structure is changed. This may explain why commercial and homemade diets containing the same ingredients may lead to different reactions in food allergic animals. Commercial diets have been compared to homemade diets for the purposes of elimination diet trials, and homemade diets have been shown superior, but these studies were done before hydrolyzed protein diets were available.

Hydrolysate Diets

Hydrolysate diets are theoretically truly hypoallergenic, whereas novel protein diets may induce adverse reactions in a subset of animals. Hydrolyzed proteins need to be smaller than 4500 Da for dogs. Most common food proteins have a mass of 10,000–70,000 Da (usually 18,000–36,000 Da). Commercial hydrolysate diets have protein fragments smaller than 5000–6000 Da. Hydrolyzed casein diets for human infants have fragments less than 1200 Da, and some infants still react at this size.

Dogs with confirmed corn, chicken, and soy allergies have been shown to tolerate corn and soy hydrolysate based diets, in most cases. In dogs with chicken allergy, hydrolysis of chicken protein led to greater than or equal 80% improvement in CADESI scores in 8/12 (75%) of the dogs. Seventy-nine percent of dogs (11/14) with confirmed soy allergy did not show skin flare-up when administered a soy hydrolysate diet. Groh and Moser (1998) found that 2//29 (69%) of dogs given a hydrolyzed casein and liver diet had reductions in clinical signs. It is worth nothing that a significant minority of dogs (up to 31%) will still react to protein hydrolysates, a fact that must be kept in mind when these diets are used diagnostically. Recent studies have shown that an accurate diagnosis of food allergy can be obtained with similar frequency using either homemade or hydrolysate based diets, but homemade diets do offer more flexibility for animals with comorbid conditions.

Novel Protein Diets

In human and veterinary practice, it is generally assumed that antigenic cross-reactivity exists, which implies that when immunologic sensitivity exists to one member of a species group, other members of that group may present a problem. This assumption has not been well tested, but most dermatologists recommend novel proteins based on this principle. To that end, beef may cross react with lamb, venison, goat, buffalo and other ruminants. Fish and shellfish commonly react with other fish and shellfish. Wheat is thought to cross react with barley and perhaps other grass grains. Cow's milk may react with goat milk but is not highly cross reactive with beef. Chicken meat and chicken egg are not highly cross reactive. Interestingly, common pollens may cross react with dietary vegetables and fruits (known as oral allergy syndrome in people). If these relationships hold true, foods containing such as rabbit, alligator and kangaroo may be superior for elimination trials using novel proteins.

Homemade Diets

Homemade diets have the advantage of flexibility, to be designed based on diet history and other disease conditions. Homemade diets also have the advantage of known ingredients. For example, commercial diets can contain undeclared ingredients, such as extenders in the vitamin supplements, processing aids and flow agents, protein preservatives for meat meals, and animal source fatty acids that may not be protein-free.

Homemade limited-ingredient diets, however, will also be nutritionally inadequate, generally in vitamins and minerals, and essential fatty acids. If the owner chooses to feed a hypoallergenic diet long term, it should be formulated by a nutritionist to include hypoallergenic supplements. In adults, the initial diet can be fed for weeks to months, but more care should be taken with growing animals and with cats.

Storage mite contamination has been suggested as a source of allergy in sensitive dogs, complicating the diagnosis when commercial diets are used. Henneveld (2006) sampled 23 bags of commercial food in Munich by examining them microscopically, and found no storage mites present.

Other Considerations for Elimination Diet Trials

Owners must be counseled on the importance of preventing ingestion of even 'small tidbits' of food.

Emphasize that even a small piece of non-allowed food can trigger a reaction. For corn, less the amount in a single corn chip is enough to derail a food trial (Jackson, 2007)! Emphasize the purpose of food challenges (to identify less troublesome, easily available but well tolerated OTC foods).

Flavored drugs and supplements can be a major confounder during the elimination diet trial. Staff should discuss each of the following with the owner, and be prepared to find hypoallergenic alternatives: heartworm preventive, toothpaste, flavored drugs such as NSAIDs and antibiotics, flavored supplements such as chondroprotectives and vitamins, and medication taste enhancers (Pill Pockets, etc).

In my experience, telling clients to avoid treats entirely is a recipe for disaster—compliance will be limited without a THOROUGH discussion of treats! Offer training treat alternatives (see resources below) where meats and grains are matched to diet. Veggies and fruits are often accepted and may be tolerated by many pets.

Environmental confounders should be addressed. If there are other animals in the house, they should be fed the same diet or separated during meals. Obviously free feeding is not acceptable unless all are fed the same trial diet! If dogs have access to cat litter boxes, antigens in cat stool have to be considered. If dogs vacuum food uncontrollably on walks, they should be leashed. Finally, if other family members are feeding meals or treats, they need to be aware of the critical—but temporary—constraints on the pet's diet.

Duration of Trial

Conflicting information exists on the proper duration of elimination diet trials, with recommendations from 3 to 13 weeks. This may support the theory that different mechanisms may be at work in different cases, with more rapid resolution and return of signs reflecting IgE-mediated disease and longer reactions suggesting IgG-mediated disease. However, GI signs are known to respond more rapidly, usually within 2 to 4 weeks.

The sacrificial diet has been recommended but is not routinely used. In my practice, it is used in many cases, based on the theory that an inflamed and hyperpermeable gut allows rapid sensitization to the new protein. The client is warned to observe for the occasional patient who will improve and then deteriorate within 2 to 3 weeks; it may be necessary to switch to another novel or hydrolyzed diet quickly at this point. I use probiotics to help reduce gut inflammation and normalize immune responses at the outset of the trial and each time the diet must be changed. In addition, I use them if the patient responds to a food challenge.

Challenges can begin as soon as maximal improvement has been reached, and occur with individual foods every 2 weeks. Some dermatologists simply recommend reintroducing the previous dog food, and if there is no reaction, the previous treats. In my view, this is not ideal because it limits the "allowed" proteins to those in the previous food and treats, and I recommend a more varied diet.

I recommend clients test foods in approximately this order, based on the need for the patient to restart medications and the ease of finding diets with these common ingredients, in this order: any essential medications that were stopped during the diet trial (like glucosamine/chondroitin); lamb, chicken, corn, fish, egg, dairy (milk or yogurt), beef, wheat (bread is a good source), turkey, and soy (tofu will do). If necessary, I also recommend they test pork, rice, and other ingredients commonly available and affordable in their area.

Prognosis

Skin signs may take up to 10 weeks to resolve after institution of an elimination diet, and can take up to 14 days to recur on reintroduction. GI signs usually resolve within 10 to 14 days, and can recur within days of reintroduction.

Tolerance to offending food allergens can be regained. Food specific antibodies disappear after a few months, but it may take 1 to 2 years before the allergen can be re-introduced. Steroids may actually suppress the generation of suppressor T cells that are vital to development of tolerance (Verlinden, 2006). Tolerance may not occur in all animals. If owners choose to feed the elimination diet long term without undergoing challenge testing, the pet can become sensitized to that protein over time. This possibility should be considered in animals that relapse.

References are available from the author upon request.

RESOURCES

Novel Meats:

- Duck
- Emu
- Ostrich
- Pheasant
- Quail
- Rabbit
- Venison
- Buffalo/Bison
- Alligator

Novel Starches:

- Tapioca/yucca
- Taro
- Sweet potato/yam
- Millet
- Quinoa
- Amaranth
- Sorghum

SOURCES FOR NOVEL MEATS AND STARCHES

Omas Pride
(fresh exotic meats such as alligator)
www.omaspride.com

Evangers
(canned meats including rabbit, duck, venison and pheasant)
http://www.evangersdogfood.com/

Wysong
(canned rabbit meat – beware as the company has started adding beef plasma to its other canned novel meats)
www.wysong.net

Addiction Foods
Unagi and seaweed
Brushtail and potatoes (with venison)
www.addictionfoods.com

Hare Today – dehydrated ground rabbit
Phone/Fax 814-587-2178
http://www.hare-today.com/
murfette@earthlink.net

PetExtras.com - ostrich tendons
30498 Wallmark Lk. Dr.
Chisago City, MN 55013
(651)257-8533
www.petextras.com

SitStay.com – rabbit ears, dried yams
5831 N 58th St
Lincoln Ne 68507
800-748-7829, 402-467-3426
Fax 402-467-5055
http://www.sitstay.com/index.shtml

Exotic Meats.com
www.exoticmeats.com
2245 148th Ave N.E.
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Toll Free:(800) 680-4375

NUTRACEUTICALS AND THERAPEUTIC DIETS – DO THEY MIX?

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Pet food manufacturers are increasingly adding functional ingredients to their formulations. While the nutritionists involved in these formulas are aware of current safety and toxicity evidence, most pet owners and many veterinarians are not. Prescription diets in particular are fed to animals with some chronic conditions, exactly the situation that initiates the owners' search for supplements in an attempt to improve their pets' condition.

Antioxidant levels are augmented in premium senior diets, arthritis diets, and in a prescription diet for cognitive dysfunction. Bjelakovic (2007) reviewed outcome studies in which antioxidants were taken by people, and found that mortality was increased. One possible reason for these poor outcomes is that generation of free radicals is an essential process for control of unwanted cells and pathogens, and if prevented, may subject the organisms to greater risks of cancer and other conditions. Alpha-lipoic acid is toxic to cats as compared with dogs or humans, and doses above 13 mg/kg may result in hepatotoxicity, anorexia, hypersalivation, ataxia, hyperirritability, and perhaps chronic accumulation with eventual toxicity at lower doses.

Specific fatty acid levels are frequently enhanced in arthritis diets, puppy foods, dermatologic and other types of diets. Studies in dogs have produced variable findings on coagulation, but platelet aggregation, serotonin release, fibrinogen concentration and antithrombin III activity were not affected by changing fatty acid ratios in a more recent study. However, Saker (1998) found that when cats were fed n-3 enriched diets (n6:n3 ratio 1.3:1) for 112 days, bleeding time was increased, and platelet activation and aggregation was lower, although activated partial thromboplastin time (APTT) and one-stage prothrombin time (OSPT) were not effected. Very high levels (100 g/day) have led to increased liver enzymes (alanine aminotransferase [ALT], aspirate aminotransferase [AST]) in humans. Increasing the total daily omega-3 intake increases the requirement for vitamin E (0.4 mg of alpha-tocopherol to 1 g polyunsaturated fatty acids [PUFA]) and perhaps other nutrients required in fat metabolism.

Glycosaminoglycans such as glucosamine and chondroitin, are used in arthritis diets and are very commonly supplemented by pet owners. The usual dose is 22 mg/kg for glucosamine HCl and 8.8 mg/kg for low molecular weight chondroitin sulfate (Neil, 2005). Occasional adverse effects in sensitive individuals and from overdose include nausea, diarrhea, and rarely, polyuria/polydipsia (PU/PD). For some time, clinicians were concerned about the potential for dysregulating diabetics; however, clinical trials have shown that these supplements do not impact glucose control in diabetes. In 2004, the Center of Veterinary Medicine (CVM/FDA) requested that the following statement go on the products that may contain GAGs (glycosaminoglycans): "Consult with your veterinarian before using this product in animals with a history of urinary tract stones," due to a theoretical concern that these molecules enhance nucleation of uroliths.

"Holistic" diets often claim to contain probiotics. Probiotics are in general are very safe, although cases of septicemia with probiotic species have been reported in gravely ill humans. Of perhaps greater concern is that fact that many of these diets do not contain viable organisms, fooling clinician and client into believing that the animal is receiving the benefits of probiotic therapy.

Other functional ingredients added to pet foods include prebiotics (as chicory or other fiber sources), carnitine, taurine, glutamine, sodium tripolyphosphate, l-tyrosine, green tea polyphenols, arginine, B vitamins, sodium and zinc. While safe upper limits (SUL) have been reviewed for essential ingredients by the National Research Council, we know less about nutraceutical ingredients. Until these levels are established, it may be wise to remember that all sources of these nutraceuticals should be kept in mind, and regular monitoring of client supplement efforts is necessary to track possibly complications.

Doses of functional ingredients in some representative diets are listed in Table 1. This table cannot represent current doses as manufacturers constantly re-evaluate and improve their formulations, so the table is provided as a starting point to help practitioners understand what is being provided in some common prescription diets. Manufacturers should be consulted to confirm current levels as needed.

References are available from the author upon request.

Table 1. Doses of Functional Ingredients in Some Representative Diets: Total Dry Diet Dose for a 25-kg Neutered Adult Dog Eating 1252 kcal Daily

Ingredient	NRC Upper Limit	Purina JM	Hill's JD	Royal Canin JS21	Royal Canin JS21 LB	Eukanuba Senior Plus	Hill's b/d	Hill's k/d	Purina NF
Glucosamine (mg)	n/a	424.75	368.75	234	468	143			
Chondroitin (mg)	n/a		247	67.8	132	13.5			
Alpha lipoic acid (ALA) (mg)	n/a		8817						
Omega-3 (mg)	3500 mg of EPA + DHA	3130	Total including ALA = 11,870			3125		5734	939
Omega-6 (mg)	20,408 (linoleic)	5509	8400			15625			8670
Vitamin A (IU)	53,333		287.25	6483	7041		4450		
Vitamin E (mg)	n/a	317		199	193		228–340*		
Vitamin C	n/a	39.5	52.5				34		
Selenium (mcg)							175		
Carnitine (mg)			113				100		

* Depending on form of Vitamin E used

NRC = National Research Council; EPA = eicosapentaenoic acid; DHA = docosahexaenoic acid.

OLD, FAT, CRUNCHY DOGS: HOW DO WE MANAGE OVERWEIGHT DOGS WITH OSTEOARTHRITIS?

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Obesity is the excessive accumulation of adipose tissue in body, and has been defined to occur when dogs or cats are more than 20% to 30% over their optimal body weight. In humans, criteria have been established for what defines "overweight" and what is "obese," and these criteria have generally been based on the body mass index. However, no similar index for optimal body weight has been identified in dogs and cats, and thus the use of these classifications has not been rigorously studied. However, in general, dogs are reported to be overweight when their body weight is 15% over their optimal body weight, and obese when they are more than 30% over the optimum. Using these criteria, the incidence of obesity in dogs and cats in the United States is reportedly between 30% and 40%. More alarming, however, is the suggestion that the incidence of obesity in our pet population is increasing despite the many attempts to control weight with diet and exercise programs.

Osteoarthritis (OA), a disease syndrome that can involve any diarthrodial joint with a synovial lining, and is the result of mechanical and biologic events that disrupt the normal balance or degradation and synthesis of joint structures, including the chondrocytes, their extracellular matrix (collagen and aggrecan) and the subchondral bone. Genetic, developmental, metabolic, and traumatic factors can initiate the process but the process is always the same: damage to cells or matrix leads to softening of cartilage, fibrillation, ulceration, cartilage loss, sclerosis of subchondral bone and osteophytosis.[13] Risk factors for osteoarthritis, in humans and in dogs, include obesity, and a common clinical presentation is the overweight dog with severe osteoarthritis.

DEFINING AND MEASURING OBESITY

The first step in the evaluation of a pet that is overweight or obese is to make an assessment of the degree of the problem. Assessment of body composition, or more specifically, attempting to separate fat mass from the lean body mass, has been approached by a wide variety of different methods, unfortunately, none are ideal. The key is to find assessment methods that are precise, accurate, easy to do in a practice setting, and not excessively costly. However, many of the tests are precise, but not accurate (able to yield the same result on repeated analysis, irrespective of accuracy), and others lack both precision and accuracy. The most precise and accurate tests that are used in research settings are costly, not easy to use and are invasive, and thus are not ideal for clinical practice. Examples of the most common research tools used for assessment of body composition include chemical analysis, densitometry, dual-energy x-ray absorptiometry (DEXA), subcutaneous or visceral ultrasonography, computed tomography (CT) or magnetic resonance imaging (MRI). Thus, in the clinical setting, the most widely used procedures to assess body composition are measurements of body weight or morphometric measurements (eg, body condition scoring). Morphometry or the measurement of form is used to assess body composition using different parameters that can be measured. Body condition scoring (BCS) employs a subjective method of quantifying the body composition based on 5-point or 9-point schemes. This system uses both visual cues and palpation of specific areas (the ribcage, waist, and dorsal spinous processes) to estimate subcutaneous and abdominal fat accumulation relative to superficial muscles. This technique is highly precise (repeatable), but not necessarily accurate. However, it is currently the most well known and repeatable means of body condition score assessment in the clinical setting and should be used as part of the physical examination of all pets presented to the veterinary clinic.

THE CAUSES OF OBESITY

The primary reason for development of obesity in any animal is that they are consuming more energy than they are expending. This can occur when a dog has excessive dietary intake of calories (food and treats) or when there is a reduction in energy expenditure (reduced activity, illness or injury resulting in less exercise). There are some medical conditions and drugs that are associated with obesity: endocrinopathies, such as hyperadrenocorticism and hypothyroidism, and drugs such as steroids and anticonvulsants. But the reason that weight gain occurs in dogs on steroids or with hypothyroidism is that they have either increased food intake or decreased energy expenditure (or in some cases, both). Nevertheless, in both instances, the development of obesity is due to a positive energy balance. While genetic factors are also likely involved (eg, Labrador retrievers have a higher incidence of obesity than is seen in other breeds of like size), the role of inheritance in canine obesity needs more study. In both dogs and cats, neutering is an important risk factor due to the hormonal changes that occur that result in changes in levels of leptin, progestins, and other hormones that result in increased appetite, and reduced energy metabolism and metabolic rate. The key factors for prevention of obesity in neutered animals appears to be careful control of intake immediately after neutering (no free choice feeding, reduction of intake by 25% to account for the hormonal changes resulting in reduced energy needs), and close monitoring of body weight and BCS to allow adjustments in intake if needed. In dogs, there are a number of dietary factors that are also associated with obesity: including the number of snacks fed, especially table scraps, and the number of meals. Dogs that were allowed to be near their owners at mealtime also had a greater tendency to be obese due to the increased likelihood of receiving table scraps and human food treats. In addition, because feeding dogs is a social interaction, feeding and food interaction with the dog can become a daily social interaction that can become a problem resulting in overfeeding and inappropriate food intake patterns. It has been shown that in households where the owners are health conscious (conscious of diet and nutrition, who exercise regularly, and watch their own weight), they tend not to have obese dogs. Thus, there are clearly human behavioral and "food is love" issues that have to be considered in the development of obesity in dogs, and these must be addressed for successful weight control to be achieved.

THE IMPORTANCE OF OBESITY AS A DISEASE

Obese humans generally do not live as long as their lean counterparts, and are much more likely to suffer from obesity-related diseases such as type II diabetes, coronary artery disease, osteoarthritis, hypertension, and some cancers. Dogs and cats are susceptible to the same detrimental effects, including decreased longevity, and development of a variety of disorders that are associated with being obese. Problems that were found to be more common in obese dogs compared to the dogs that were of ideal body condition, include heat intolerance, increased anesthetic risk, increased difficulty with routine clinical procedures (catheter placement, palpation, imaging), and prolonged surgical procedures.

In order to understand the role of obesity in disease development, it is necessary to first understand the role of adipose tissue in energy balance and metabolism. The expansion of adipose tissue was long thought to be simply a depot for the deposition of fatty acids (triglycerides) that occurred because of the excess energy intake. However, research in the past decade has revealed that adipose tissue is not just a storage site, but also is responsible for production of many key hormones (eg, leptin) involved in energy balance and a variety of other processes. Leptin was first identified in 1994 and its discovery opened the door to a whole new world of understanding about white adipose tissue. Leptin is an inhibitor of food intake—primarily through suppression of neuropeptide Y and orexin in the brain, and plays a role in the regulation energy expenditure. In obese mice that lack leptin or have leptin resistance, appetite suppression mechanisms are nonfunctional and energy metabolism abnormal. However, despite the importance of leptin in appetite suppression and energy expenditure, it is not the "silver bullet" of obesity management: simply replacing leptin does not result in weight loss or changes in the metabolism of obese animals. Further research in recent years has elucidated an entire list of adipokines secreted by fat cells. These adipokines are involved in a wide variety of metabolic and physiologic, as well as inflammatory changes that are implicated in the pathophysiology of obesity. Why did it take so long to understand the importance of fat cells in disease? The key reason is their apparent simplicity—in histologic appearance as well as metabolically—that belied their important role in energy metabolism and as an endocrine organ. Adipose tissue is a major secretory organ and does not just release fatty acids during fasting—the tissue also releases a wide variety of lipid-based moieties: cholesterol, retinol, steroid hormones and prostaglandins. However, fat cells also secrete many pro-inflammatory cytokines (eg, tumor necrosis factor alpha was the first to be discovered), including interleukins (IL-1, IL-6, IL-10), chemokines (such as monocyte chemoattractant protein-1), proteins involved in hemostasis (platelet activator inhibitor-1) and blood pressure (angiotensinogen). What does this mean for the obese dog? Obesity is a metabolic disease that results in major changes in appetite control, energy expenditure, and induces a chronic, low-grade, pro-inflammatory state that may be responsible for many of the diseases associated with increased body weight.

There are a number of diseases in dogs and cats are reported to be associated with obesity, including orthopedic diseases, diabetes, heart disease, abnormal circulating lipids, certain cancers, urethral sphincter mechanism incompetence, dyspnea due to compromised ability to breathe (eg, laryngeal paralysis, brachycephalic syndrome, tracheal collapse), heat intolerance, decreased immune function, and dystocia to name just a few. Further, we do not have a complete understanding of the inflammatory role of obesity hormones in our pets, and this could lead to an even greater connection between obesity and disease. Finally, as we have previously shown from the prospective study of calorie-restricted dogs, dogs that are obese also do not, on average, live as long as their leaner counterparts. The bottom line is that prevention of obesity in dogs can increase both the quality and quantity of their life.

HOW DOES OBESITY AFFECT OSTEOARTHRITIS?

Work done by the Purina Nutrition Research Department in conjunction with other co-investigators provided the first objective data in veterinary medicine demonstrating overweight as a risk factor for OA in a well-designed and controlled longitudinal study.[15-20] In this paired feeding study, 48 Labrador retrievers were paired by sex and weight within litters (litters from 7 dams and 2 sires) and randomly assigned to a control-fed group or a limit-fed group that received 25% less food than the control-fed group. Radiographic evaluation of the prevalence and severity of OA in the hip, shoulder, elbow and stifle joints when the dogs were 8 years of age were compared. Osteoarthritis was present in the hip joints of 15 of 21 versus 3 of 21 control versus limit-fed dogs, in the shoulder joints of 19 of 22 versus 12 of 21 of the control versus limit-fed dogs, and severity, not prevalence, of OA in the elbow joint was greater in the control-fed group. As these dogs were followed until they died, limit-fed dogs lived almost 2 years longer than the control-fed dogs, and interestingly, musculoskeletal disease (OA and lumbosacral disease) were the leading causes of debilitation leading to euthanasia in 26 of the 48 dogs, with roughly equal numbers in both feeding arms of the study. However, musculoskeletal diseases resulting in death in the control fed dogs were at a mean age of 10.6 years versus 13.1 years in restricted-fed dogs. Data from these dogs looking specifically at hip

OA showed that restricted-fed dogs had a lower prevalence and later onset of hip OA, with radiographic signs starting at 6 years versus 12 years in the control versus restricted-fed dogs. By 14 years, 83% of the control-fed group had radiographic evidence of hip OA, versus 50% of the restricted-fed group.

DIETARY THERAPY

So we know that restricted feeding can help reduce the severity and prevalence of OA in dogs with a genetic predisposition. What about the overweight dog with OA that presents to us in our practice? Is it too late, or will weight loss help? Although it has always made good common sense that weight loss should improve lameness in dogs with osteoarthritis, the first study to actually demonstrate this was published in 2000.[14] Nine overweight (not obese) client-owned dogs with radiographic and clinical signs of hip osteoarthritis were fed a 60% calorie-restricted diet and evaluated over 10 to 19 weeks or until they had lost at least 10% of their body weight, with at least one midpoint evaluation. Evaluation techniques included body weight, body condition score (1–5), a numerical rating score for lameness at the walk and trot, a numerical rating score for palpation of the hip joints, and a 100 mm visual analog score at the walk and trot. All parameters scored were significantly different (improved; $P<0.05$) by the end of the study.

There are two important goals in establishing an appropriate dietary therapy regimen: 1) it must be tailored to the individual animal (diet needs for allergy, renal disease, GI issues, etc.), and 2) caloric restriction must occur without concurrent protein starvation to prevent loss of lean muscle tissue during weight loss. The first step in making a diet plan is to obtain a complete dietary history that gives an accurate accounting of all foods fed to a pet on a typical day. In some cases, it may be necessary to have the owners keep a diet log for a week, writing down the meals, the treats, the table foods, and so on consumed by the dog during that time. This is especially helpful in households where the dog may receive foods from more than one individual (especially children). In addition, it should be noted if the dog has access to any other foods (other pets in the family, outside scavenging), if the pet received medications in foods, and if there are other food items available to the dog (chew treats, dental chews).

The next step in designing a diet plan is to decide upon a weight loss goal. The goal does not necessarily have to be that the pet achieves its ideal body weight – this goal should be based on the pet, the owner's situation and goals, and the ability to reach the goal. It is important to set reasonable goals that can be achieved, rather than overly ambitious goals that are not likely to be achieved and result in the client becoming discouraged because their pet is not meeting the expected goal. A step-down approach to weight loss is much more likely to result in success and continued owner persistence, than a goal that is too ambitious and results in the owner abandoning the process due to lack of progress. Once you have set the appropriate weight loss target for that pet, then you can calculate the energy restriction that will be required to achieve the goals you have set. Ideally, the best way to set the new energy intake is to reduce intake to 60% to 80% of the pet's current intake. If the pets intake is not known (or cannot be calculated accurately), then it is necessary to calculate an estimate of intake for the target weight. There are a number of different equations recommended for calculating maintenance energy requirements. Finally, another way that you can calculate calorie reduction is to calculate the energy content of the amount of fat mass you wish the pet to lose (eg, 1 kg adipose tissue = 7700 kcal). Take this number and divide by the number of days you plan to feed the weight reduction diet. That number is subtracted from the dog's current intake to achieve a new, lower number of calories for intake. This method is more cumbersome, but is based on a more precise estimate of fat loss. Nevertheless, no matter which approach is used, the key to success is first to have complete client cooperation, then to monitor the pet frequently (eg, every 3–4 weeks), and finally to make adjustments in intake as needed based on the plan you have developed. To be sure of accuracy in the weight loss period, it is important to weigh the pet on the same scale. To provide safe, but efficient weight loss, the dog should not lose more than 1% to 2% of its body weight per week.

In addition to reducing the energy intake of pets that are overweight, it is also possible to increase weight loss by increasing energy expenditure through increased exercise. In obese dogs, as in obese humans, it is important to start slow with an exercise program, and only very gradually and slowly increase the duration and intensity of the exercise. In some dogs, exercise may be impossible, due to severe joint problems or exercise intolerance or due to inability of the owners to exercise with their pet. In these dogs, very minimal activity, or low impact activity, such as a treadmill or water treadmill may be needed to allow safe, non-painful activity. Consultation with a veterinary physical rehabilitation specialist is often very helpful in determining appropriate activities for the dog. This can also be part of the overall diet and weight reduction plan, as the weigh-ins and evaluation of the pet's progress can occur in conjunction with the visits to the rehabilitation program.

WHAT ABOUT JOINT DIETS AND SUPPLEMENTS?

Clearly, weight loss is one of the cheapest and most sensible things that we can prescribe for overweight patients with OA. There is zero expense and the only side effects may include behavioral change (begging, stealing and driving owners crazy: see below). The role of the diet itself is not so clear; however, there has recently been a proliferation of "joint diets." It is important to note that these are not formulated as weight loss diets, so a careful evaluation of daily caloric intake must be made. These diets rely on the incorporation of an increased ration of n3 fatty acids versus n6 fatty acids. There is evidence to suggest that n3 fatty acid supplementation can have a positive effect on cartilage and its metabolism as metabolism of n3 fatty acids incorporated into the cell membranes shifts the conversion of arachidonic acid to a less inflammatory pathway. While there are no randomized, controlled clinical trials published evaluating the role of n3 fatty acid supplemented diets, there are some data to suggest that it does improve lameness in experimental models of OA in the dog.[13]

The use of other dietary supplements to improve clinical signs of osteoarthritis in the dog is not clear. The use of antioxidants, such as MSM, vitamin E, and vitamin C, has not been evaluated in dogs. Chondromodulating agents, such as chondroitin sulfate, often in combination with glucosamine, have shown conflicting results in clinical trials in humans and are the subject of controversy and the same is true in dogs. One study showed no efficacy when compared to meloxicam and carprofen,[24] while another demonstrated a statistically significant improvement in pain, weight-bearing and severity of the condition as evaluated by veterinarians by day 70 in a randomized, double-blind, controlled, multi-center trial conducted in the UK and Ireland.[21]

The investigators used a formulation containing glucosamine HCl 475 mg/g, chondroitin sulfate 250 mg/g, N-acetyl-D-glucosamine 50 mg/g, ascorbic acid 50 mg/g, and 30 mg/g of Zn sulfate. Treatments were assigned on the basis of body weight at the rate of 1 g of active ingredient twice daily to dogs weighing 5–19.9 kg; 1.5 g twice daily to dogs 20–40 kg, and 2 g twice daily to dogs weighing >40 kg for 42 days. After 42 days, the daily dose was reduced by one third for the subsequent 28 days. Carprofen was given at 2 mg/kg twice daily for 7 days followed by a loading dose, followed by 2 mg/kg once daily for the remainder of the study, with the second "dose" actually a mannitol-filled placebo. Animals were reassessed on days 14, 42, 70 and 98, and treatment was stopped on day 70. While carprofen was, predictably, effective on various parameters measured throughout the study, the nutraceutical was only effective at day 70, suggesting a longer time to efficacy and a relatively short effect once the supplement was stopped.

ROLE OF PHYSICAL REHABILITATION

To effect weight loss, diet must be balanced against exercise. Dogs who are painful and overweight are reluctant to exercise, and owners often note that these dogs really "pay the price" after vigorous, particularly high impact (running, jumping) exercise. Alternatives include low-impact exercises, such as walking and swimming. The proliferation of animal rehabilitation centers and programs at many referral practices and university hospitals has improved owner access to therapies such as water treadmills, and techniques like heat and cold therapy, passive range of motion, and active range of motion exercises, many of which can be learned and practiced at home. Although the literature is only in its infancy in the area of small animal rehabilitation, a recent study evaluated the effects of a weight loss program with two types of physical therapy programs on overweight dogs with OA.[22] In this non-blinded prospective randomized trial, 29 adult overweight or obese dogs with a BCS of 4/5 or 5/5 and clinical and radiographic signs of OA were assigned calorie restriction and either a moderate, home-based rehab program or a more intense, hospital-based rehab program. Lameness was assessed clinically and by force plate analysis. Both groups lost weight, however, greater weight reduction was noted in the group with more intense physiotherapy. Mobility and force plate analysis were improved in both groups at 6 months, but the intensive group had the better outcome, demonstrating that exercise in combination with diet in obese dogs with OA can be accomplished and has demonstrable positive effects.

Many dogs become obese due to the social bonding that occurs with owners and their dogs during feeding. This human–animal bond activity results in a strong behavioral component to the development of obesity that must be addressed. In order to achieve success in changing these behaviors, it is important to substitute low-calorie treats, games, or grooming activities for table scraps or other high calorie treats. Begging for food is more of a behavioral problem than a hunger problem, and if this relationship is not considered in weight loss programs, the plan is doomed to fail. In some cases, consultation with a veterinary behaviorist is an important part of the overall plan for weight loss.

PHARMACOLOGIC OPTIONS FOR OBESITY MANAGEMENT

In addition to traditional therapies used for weight regulation or weight loss, there is increasing interest in other modalities (drug therapy, surgical options, nutraceuticals) that may improve the odds of success. There are currently three different pharmacological approaches to weight management currently available for use in humans: 1) drugs that reduce fat digestion from the intestine, 2) drugs that reduce appetite, and 3) drugs that increase metabolism (fat burning). These have been previously reviewed and are not discussed here. There is one drug approved for use in the United States (and one in Europe) for weight loss in dogs (another one is in the approval process), and that is dirlotapide (Slentrol®, Pfizer Animal Health), a selective (intestinal) microsomal triglyceride transfer protein (MTP) inhibitor that works primarily by preventing formation of chylomicrons in intestinal cells, an effect that induces an increase in peptide YY secretion. Peptide YY is a potent appetite suppressant whose effect is on the satiety center in the hypothalamus, and this accounts for 90% of the action of the drug. The reduction of fat absorption in the small intestine that results due to prevention of formation of chylomicrons is responsible for only a small fraction of the effect, and thus steatorrhea and other side effects related to fat malabsorption are minimal. Because of the difficulty in achieving weight loss in extremely obese dogs, it is likely that pharmacologic options for obesity management will become an increasingly important part of the overall approach to the problem.

SURGICAL OPTIONS

Although surgery is not an option for many dogs, addressing the underlying disease in dogs with joint replacement (hip, elbow, stifle) or correcting instability (stifle) is a well-accepted management for OA and may break the pain cycle sufficiently to allow dietary therapy and exercise to work on the overweight problem. Interestingly, a recent case report documented the effective use of minimally invasive liposuction to achieve initial weight loss (10%) in a 14-year-old dog with giant lipomas and severe hip osteoarthritis.[23] In this case, surgery provided acute weight loss and the owners were able to continue with further dietary weight loss and exercise, with improvement noted based on activity, weight loss and reduced need for NSAID at one year after surgery.

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PERCUTANEOUS ASPIRATION OF THICKENED INTESTINAL WALL FOR THE DIAGNOSIS OF INTESTINAL LYMPHOMA IN CATS

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Intestinal lymphoma is a relatively common cause of chronic weight loss, vomiting, diarrhea, and anorexia in middle-aged and older cats. This discussion covers a diagnostic technique for obtaining cytology samples of the intestine for the diagnosis of intestinal lymphoma.

SUSPECTING CATS WITH INTESTINAL LYMPHOMA

When metabolic diseases such as chronic renal failure, hyperthyroidism, and diabetes mellitus have been ruled out by appropriate blood and urine testing, then often a gastrointestinal illness is suspected as the cause for the exhibited signs of disease.

On physical examination, these cats often are quite thin, and a thorough abdominal palpation can be accomplished quite easily. Special attention should be paid to the character of the intestinal loops during abdominal palpation. In normal cats, the intestinal loops can be felt passing through the examiner's hand rather indistinctly, because they are thin and flat, analogous to a flattened firefighter's hose. In a cat with an infiltrative intestinal disease such as lymphoma, the intestinal loops are quite distinct during palpation, round and firm, analogous to a vinyl garden hose which is always in a circular shape. Some cats with intestinal lymphoma may have a large mass associated with a loop of bowel, or may have enlarged abdominal lymph nodes that can be palpated during examination.

TESTING FOR INTESTINAL LYMPHOMA

Several diagnostic pathways can be taken to identify intestinal lymphoma. Abdominal radiographs are seldom helpful, since decreased body fat makes for poor abdominal contrast. Abdominal ultrasonography can assist in identifying abdominal lymphadenopathy, quantifying intestinal wall thickness, and localizing and specific masses associated with the intestinal tract. Ultrasound-guided aspiration of lymph nodes, masses, or thickened areas of the GI tract can also be performed.

Upper gastrointestinal endoscopy is another excellent approach for the diagnosis of intestinal lymphoma. Good technique (ie, ability to enter the duodenum) is required to acquire diagnostic specimens, and occasionally the neoplastic infiltrate is in the submucosa, making endoscopic samples nondiagnostic.

Exploratory laparotomy and full-thickness intestinal biopsies are the gold standard for diagnosis. Most cats, however, are already somewhat debilitated and tissue healing can be a problem. Additionally, treatment with corticosteroids or chemotherapy may need to be delayed if a surgical wound needs time to heal.

PERCUTANEOUS ASPIRATION OF THICKENED INTESTINAL WALL

The technique of percutaneous aspiration of a thickened intestinal wall can be used alone or in conjunction with another diagnostic test to help diagnose intestinal lymphoma. It attempts to collect cells from the muscular and submucosal layers of the intestine, so it can complement the diagnostic information provided from endoscopy (which provides information primarily from the mucosal layer).

Although this technique can be done using ultrasound guidance, it is not required (or, in the case of this author, preferred). This makes percutaneous aspiration of thickened intestines a less expensive way to obtain cytologic samples when ultrasound is not available or is not financially feasible for an owner.

To perform the aspiration, the patient is anesthetized with an appropriate short-acting anesthetic such as propofol. The patient in placed in lateral recumbency and the abdomen is again thoroughly palpated to identify any masses, differentiate thickened small intestinal loops from fecal material in the colon, and select an appropriate intestinal loop for aspiration. The selected loop should be freely moveable, thickened, and able to be mobilized near the body wall. Once the intestinal loop has been selected, the site over the intestinal loop should be clipped and surgically prepped with chlorhexidine scrub and alcohol. Once again, the intestinal lop should be mobilized and held to the body wall, just below the skin, in the prepped area.

A 22-gauge needle attached to a 3-mL syringe should be used for the aspirate. The needle should be introduced parallel to the long axis of the intestine, at about a 30 degree angle. The depth should be estimated to reach the wall of the thickened gut loop. Once in place, several aspirations with the syringe plunger are taken, and then negative pressure is released. The syringe and needle are removed, and the intestinal loop released.

The sample is routinely prepared by placing on a slide and gently spreading with a second slide. Four to six slides should be made from one aspiration. One slide should be checked immediately after staining to ensure the adequacy of the sample. If it contains only fat, then the aspirate was too superficial; if it contains debris and bacteria, then it penetrated the lumen and contains intestinal contents. In either case, the aspirate should be repeated to obtain a diagnostic sample for cytology. Penetration of the lumen with a 22-gauge needle is unlikely to cause harm. If an abdominal mass or lymph node is palpable, it can be aspirated in a similar manner.

In this way, diagnosis of many cases of intestinal lymphoma can be made. Risks are relatively small, and costs are minimal.

MAMMARY GLAND TUMORS: YOUR QUESTIONS ANSWERED

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Despite the fact that mammary tumors are commonly encountered in veterinary practice, little progress has been made in the clinical management of mammary carcinoma in recent years. Of all neoplasms in female dogs, breast tumors represent 25% to 50%, and are the second most frequent class of neoplasm seen in dogs after skin tumors. In the cat, mammary glands are the third most common site of cancer after hematopoietic and skin tumors. Half of all dogs presented with mammary masses in veterinary practice will have benign disease that is surgically cured with ease. Of the 50% of dogs that present with mammary malignancy, a further one half are cured by adequate surgery. Thus 75% of dogs with mammary masses are cured with relatively straightforward management approaches. Veterinary oncologists and general practitioners face a twofold challenge with regard to mammary tumors. First, criteria must be established and accepted that identifies the 25% of dogs at risk of death from malignant mammary disease, so that more intensive therapy can be used to improve survival for this group. Progress has been made in this area, and several studies identifying prognostic factors will be summarized here. The second challenge, which has been less well addressed in recent years, is to develop better treatments for aggressive mammary cancer in the dog and cat.

PROGNOSTIC FACTORS

Age, Breed, and Sex Factors

The median age of dogs with mammary tumors is 10 to 11 years. Female sex is a strong predilection factor, with mammary tumors rarely seen in male dogs (approximately 1% of malignant mammary tumors in one study were seen in males). Mammary tumors in males they tend to be highly malignant. While reproductive hormone status appears not to be related to prognosis once mammary tumors have developed, the most widely accepted risk factor for developing mammary carcinoma in the dog is the number of estrous cycles in bitches before spaying. The risk in neutered bitches for developing mammary tumors is only 12% of the mammary cancer risk for intact bitches. Bitches spayed before the first heat cycle had a relative risk of 0.05% for mammary cancer, while those with 1 heat cycle had 8%, and those with 2 or more cycles had 26% relative risk. After 2.5 years of age or 4 estrous cycles the sparing effect of ovariohysterectomy is lost.

Tumor size is of prognostic significance. In a study of 253 dogs with mammary tumors, there was significant difference in survival between groups of dogs when primary tumors were classed as <5 cm, 5–10 cm, 11–15 cm, and >15 cm in diameter. A more recent study confirmed this finding, with tumors of less than 3 cm diameter having significantly better prognosis than tumors greater in size. This size effect was lost if the primary tumor was associated with lymph node metastasis or vessel invasion, however.

Dogs that are obese may have poorer survival when surgically treated, but the risk of developing breast cancer in obese versus thin dogs was not clearly different, as happens in women. However, one study suggested that dogs fed low fat diets (< 39% of dietary calories derived from fat) had a significantly better prognosis for 1 year survival after surgical removal of mammary tumors, particularly if also on a high protein diet, than those dogs fed higher fat diets regardless of protein content.

Inflammatory carcinoma carries the worst prognosis of all the histologic subtypes of mammary cancer, and is generally metastatic at presentation. Dogs with inflammatory carcinoma have warm, painful tumors often associated with thickened, ulcerated skin and lymphedema in the nearest limb. This condition can mimic mastitis, and dogs may be clinically depressed with nonspecific signs of illness when affected by inflammatory carcinoma. Biopsy is warranted to distinguish infectious from neoplastic cause of this condition, but mastectomy is rarely curative in inflammatory carcinoma. If surgical resection of the primary lesion is attempted, it is common to see tumor nodules recurrent in the incision line at the time of suture removal.

FELINE MAMMARY TUMORS

Cats present with an overall more aggressive form of mammary cancer than what is seen in dogs. When a mammary mass develops in a feline patient, it is 80% to 90% likely to be malignant, with the majority of these tumors being adenocarcinomas. Median age at onset is 10 to 12 years, and Siamese cats have an increased risk of mammary tumor development, with an earlier age at onset than other breeds. Association with age at spaying has not been made for the disease in cats. Mammary carcinoma cells from cats are more likely to express progesterone receptors, and cats treated with progestational drugs are more likely to develop mammary carcinoma. Most feline mammary cancers are locally invasive and have lymphatic infiltration. Size of tumor is prognostic, in that cats with smaller tumors have longer disease-free intervals and survival times.

HISTOPATHOLOGIC EVALUATION

Several histopathology classification systems have been developed to better define the prognosis in dogs with mammary malignancies, but none is universally accepted. The pathology of these tumors is complex and tumors are heterogeneous, so exact classification of tumors can be difficult. In most studies, epithelial tumors that are more highly differentiated (those with acinus and tubule formation) and tumors with few mitotic figures and more regular nuclear size and shape are associated with a more favorable prognosis.

The most recently published classification system, reported by Kurzman and Gilbertson in 1986, seems to correlate well with biologic behavior of tumors. Using this system, tumors classified as benign with moderate to marked cellular atypia revealed dogs had a nine-fold higher risk of later developing invasive carcinoma than those with benign mastopathy without atypia. Also, this system allows for histologic staging of tumors based on extent of disease, which proved to be of prognostic value. Degree of nuclear differentiation within these histologic stages further helped to identify subsets of patients. More aggressive tumors were associated with less nuclear differentiation, and tumors with better overall prognosis tended to be those with well-differentiated nuclei. This effect of nuclear differentiation was most apparent in dogs with Histologic Stage I disease, in that recurrence rates within 2 years of mastectomy were 77%, 63%, and 40% for poorly, moderately, and well-differentiated Stage I tumors, respectively. Lymphoid cellular reactivity was a positive correlate for prognosis, in that dogs with tumors infiltrated with lymphoid cells had a threefold decreased risk of recurrence or metastasis within 2 years of surgery, as compared to dogs whose tumors failed to elicit such an immune response. The final correlate with prognosis in this study was presence or absence of lymph node involvement with carcinoma; dogs with metastasis to regional nodes had a poor prognosis, regardless of other factors.

Another classification system based on descriptive morphology of tumors in 253 surgically treated dogs, refers to "complex" tumors (mixed tumors with both secretory and myoepithelial components) and "simple" tumors (only one cell type present). These subclasses were correlated with prognosis. Patients with complex carcinomas survived better and those with simple carcinomas or sarcomas. In this study, 63% of bitches with malignant mammary tumors died or were euthanatized because of recurrent or metastatic tumors within 2 years of surgery.

A large series of surgically treated dogs (320 bitches) in Great Britain reported by Bostock, was subjected to classification by histopathologic morphology and correlates with survival time were reported. Dogs with benign tumors had a median survival time of 114 weeks as compared with 70 weeks for those with carcinoma. More than half the dogs with mammary carcinoma were surgically cured, and those that were destined to die of their malignancy did so within 1 year of surgery. Of the dogs that died of cancer, the pathologic description of the tumor and degree of invasiveness was correlated with length of survival.

A common assay in human medicine detects the level of hormone receptors for estrogen and progesterone in breast tumors. In women, tumors with high levels of cellular hormone receptors tend to be better differentiated and therefore to carry a better prognosis. Also, patients with hormone receptors present on their tumors are more likely to respond to hormone therapy. In the dog, limited studies have revealed that 50% to 60% of canine mammary tumors are positive for estrogen and progesterone receptors; as is the case in women, the better-differentiated tumors are more likely to be receptor-positive. A recent limited study revealed that dogs whose tumors expressed estrogen or a combination of estrogen and progesterone receptors had longer survivals than those dogs whose tumors expressed progesterone receptors alone, while dogs that failed to express detectable hormone receptors had the poorest survival

THERAPY

Surgery

Surgical excision is the most curative modality for treatment of local breast neoplasia. Some controversy exists as to the best form of surgical therapy. Traditionally in veterinary medicine, five surgical approaches have been used for canine mammary neoplasia, ranging from: mass excision ("lumpectomy"); removal of the affected gland (simple mastectomy); removal of the tumor, gland, intervening lymphatics and regional nodes (en bloc resection); removal of the gland and adjacent glands plus lymphatics (half chain resection); and removal of the entire chain of glands plus regional nodes (unilateral mastectomy) (Table 1). Radical or whole chain excision has been demonstrated to provide no survival advantage over excisional biopsy with 2 cm margins in the dog. Less extensive surgery is associated with less morbidity and more rapid recovery, but more extensive surgery may prevent the onset of de novo tumors by reducing remaining glandular tissue and thus may be more cost effective in the long term. More extensive surgery also allows for more thorough evaluation to detect lymphatic and venous invasion, multicentric carcinoma in situ, and the regional lymph nodes for metastatic disease.

Ovariohysterectomy has been advocated at the time of mastectomy. Traditional studies have demonstrated no advantage in terms of duration of survival, local recurrence rates or distant metastasis in dogs spayed at the time of mastectomy. However, since 50% to 60% of canine mammary malignancies have receptors for hormones (estrogen or progesterone), removal of the hormone source may be helpful for a subpopulation of cases. This hypothesis was born out in a study conducted at The University of Pennsylvania by Sorenmo et al. In this study, 145 dogs with malignant mammary tumors were analyzed retrospectively. Dogs that were spayed at any time lived significantly longer than intact dogs (median survivals 470 vs. 198 days). Twenty-two dogs were spayed at the time of mammary gland removal and these dogs had a median survival time of 563 days. Dogs that had been spayed > 2 years before the diagnosis of mammary carcinoma (N = 34 dogs) had a median survival time of 331 days. The hypothesis for this study was that tumors grown in a hormone rich environment are more likely to have hormone receptors than tumors grown in a hormone poor environment. Ovariohysterectomy concurrent with mammary gland removal would therefore have a

Table 1. Surgical Approaches for Canine Mammary Neoplasia

Tumor	Surgical Technique
<5 mm, encapsulated, moveable	Lumpectomy
Central location, one gland	Mammectomy
Multiple adjacent glands or between glands	Regional mastectomy
Numerous tumors throughout chain	Unilateral mastectomy
Numerous tumors in both chains	Bilateral mastectomy or staged unilateral (3–4 weeks apart)
Fixed to underlying tissues	Radical mastectomy

greater impact on these dogs, and leaving dogs intact after mammary tumor removal would allow more stimulation to receptor-positive tumors with early relapse and metastasis the expected outcome. Ovariohysterectomy also prevents other reproductive tract diseases such as pyometra and oviarina neoplasia.

In cats, surgical excision is the treatment of choice for local control. Unilateral or bilateral radical mastectomy has been demonstrated to lead to longer disease-free intervals but not necessarily longer overall survival times. Cats frequently develop local recurrence after mastectomy; it is not uncommon to manage these by multiple surgeries before eventual metastasis.

ADJUNCTIVE AND PALLIATIVE THERAPY

Radiation Therapy

No published studies demonstrate the efficacy of radiotherapy in prolonging survival or preventing local recurrence for canine or feline mammary malignancy. It is very likely that local radiotherapy would prove helpful in a palliative setting for select cases, especially in inflammatory carcinoma. Further studies are indicated to evaluate the benefits of adjuvant radiotherapy in canine patients.

Chemotherapy

Chemotherapy for women with mammary carcinoma is an established treatment. Drugs that have the greatest efficacy in women are cyclophosphamide, doxorubicin, methotrexate, and fluorouracil. Note that fluorouracil is contraindicated for use in cats because of fatal neurotoxicity. In the dog, very limited information has been published to support the use of chemotherapy. Doxorubicin (30 mg/m^2 Body Surface Area [BSA] IV every 21 days, maximum 8 cycles of therapy) and mitoxantrone (Novantrone™, Lederle Laboratories, 5.5 mg/m^2 BSA IV every 21 days) have shown efficacy in inducing remission in dogs with advanced mammary cancer. Little information is available regarding the use of chemotherapy in an adjuvant (micrometastatic disease) setting in dogs. The issue of treatment of micrometastatic disease in an adjuvant setting, which might ultimately lead to cures for some patients, cannot be adequately addressed until better clinical trials of chemotherapy for gross disease have been carried out for canine and feline patients. Doxorubicin and cyclophosphamide have been demonstrated to be effective as an adjuvant therapy to palliate advanced mammary carcinoma in cats.

Hormone Therapy

The drug tamoxifen (Nolvadex™, ICI Pharma) and is useful in an adjuvant or advanced disease setting in human patients. Tamoxifen is a nonsteroidal anti-estrogenic compound, capable of binding tightly to cytoplasmic estrogen receptors. The drug has estrogenic effects in some tissues, as well as anti-estrogenic effects. The distribution of tissues responsive to the agonist effect and antagonist effect of tamoxifen appears to be different in canine patients than in human patients, which may account for a difference in the efficacy as well as in the adverse effect profile. The anticancer effect of tamoxifen in treating mammary malignancy may be mediated by mechanism other than estrogen receptor binding, including alteration in signaling through other growth factor receptors and modulation of protein kinase C activity. Thus, it is possible that even estrogen receptor negative tumors may undergo remission when treated with the drug.

Because of difficulty of performing routine estrogen and progesterone receptor assays in dog tissue, hormone therapy has not been established for treatment of canine mammary tumors. A study of tamoxifen for treatment of mammary carcinoma in 16 dogs was performed by Kitchell et al. Nine dogs were treated in an adjuvant setting with mammary tumors considered at high risk of relapse based on histologic criteria, and 7 dogs had nonresectable or metastatic disease. In this study, tamoxifen (2.5–10 mg, mean dose 0.42 mg/kg BID PO) was shown to be effective in reducing tumor burden in 5 of 7 of dogs with nonresectable or metastatic mammary carcinoma. Side effects were seen in these 16 dogs including vulvar swelling, vaginal discharge, urinary incontinence, urinary tract infection, clinical signs of estrus, mental "dullness," and partial alopecia. The most significant side effects seen were pyometras; one intact female had a closed-cervix pyometra that required surgical intervention and three recently spayed bitches had stump pyometras that were managed medically. The authors suggest that the stump pyometras occurred because of inadequate time for involution of the cells in the uterine cervix, and for that reason they recommend that dogs have been spayed at least 2 months prior to instituting tamoxifen therapy. This limited study indicates a potential role for tamoxifen therapy in the management of canine mammary carcinoma. Newer, more targeted selective estrogen receptor modulators (SERMS) have been developed in human medicine and need further exploration in veterinary medicine.

MAST CELL TUMORS

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CANINE CUTANEOUS MAST CELL TUMORS

Canine cutaneous mast cell tumors (MCT) are a challenge for the veterinarian. Tumors occur in older dogs (mean age 9 years), but any age may be affected. There is no sex predisposition. Flat-nosed English breeds (Boxers, Boston terriers, Bullmastiffs) have a hereditary predisposition. Shar Peis appear to be prone to a particularly aggressive variant. Boxers and possibly golden retrievers tend to have well-differentiated tumors, according to some authors. While the exact etiology of canine mast cell tumors remains unknown, several factors have been implicated over the years. An early study suggested a viral etiology, based on the observation of apparent cell-free transmission of mast cell disease in experimental dogs. No infectious etiologic agent has ever been identified, however. The role of genetic factors and exposure to environmental carcinogens is probable.

Clinical Signs

Most tumors in dogs are solitary, but 10% can present as multiple cutaneous lesions at initial diagnosis. Originally, the presence of multiple concurrent tumors was thought to be a negative prognostic sign, but recently studies have shown that many of these dogs enjoy long-term survival. Most tumors are discovered as a cutaneous or subcutaneous mass with no overt clinical signs. These tumors have a varied appearance and are often mistaken for benign lipomas, skin tags, or cysts. They may be present for many years without changing in size. Alternatively, tumors may degranulate when touched or manipulated, releasing the contents of inflammatory granules. Owners may notice dramatic differences in tumor size over short periods of time due to this swelling and resolving phenomenon after degranulation. Additional paraneoplastic signs associated with release of vasoactive substances are detailed below.

Staging

Staging for mast cell tumors involves grading the local tumor, assessing regional lymph nodes, and distant sites such as liver and spleen. In the dog, 50% of ast cell tumors are benign and cured by surgery. However, an additional 50% are malignant. Malignant mast cell tumors can recur locally or can become metastatic, with the higher histologic grades of tumor associated with more aggressive behavior. Historically, the published literature and text references recommend that mast cell patients be staged with thoracic radiographs, abdominal ultrasound, liver and splenic fine needle aspirates, bone marrow aspiration, and buffy coat analysis. However, in February of 2000, the Veterinary Cancer Society hosted a focus meeting about canine mast cell disease. At this meeting, changes in staging protocols were recommended. These recommendations were based on the observation that buffy coat blood tests for mast cell leukemia, ultrasound evaluation for liver and spleen involvement, and bone marrow analysis yielded less that 2% positive results in a large series of more than 100 cases. Mast cell tumors that are destined to become metastatic are generally the Grade III tumors, particularly those of axillary and inguinal or preputial location, and the most fruitful site for staging evaluation is the regional node.

Prognostic Factors

Prognostic factors include the location of the primary tumor, in that tumors of the inguinal, axillary, and perineal region may be more aggressive than those arising on the lateral trunk, head or extremities. Histologic grades are associated with outcome; the high-grade tumors are more likely to be metastatic and have shorter overall survival times. In the classic study of cases treated at The Animal Medical Center, 93% of patients with surgically excised Grade I tumors survived 1500 days (approximately 4 years), while 47% of Grade II and 6% of Grade III tumors treated with surgery alone survived for this period of time. Overall, around 50% of all patients in this study were cured by surgery.

Paraneoplastic Disorders

Paraneoplastic disorders caused by MCT include problems associated with degranulation, such as gastroduodenal ulcers from histamine release, coagulopathies from heparin release, and delayed wound healing due to release of proteolytic and vasoactive substances. Management of the paraneoplastic complications of mast cell tumors includes treatment of the primary tumor site, and also symptomatic and direct therapy to counteract the substances released during degranulation. H2 antagonists such as cimetidine, and the coating agent sucralfate, may be used for dogs with ulcers. Fecal occult blood tests may be helpful in determining subclinical ulcers, but the tests must be performed with care using a meat-free diet before testing to avoid false positives. Protamine sulfate, a heparin antagonist, has been reported to be helpful for prolonged hemorrhage, especially for procedures such as splenectomy. Antihistamine and H2 antagonists reportedly aid in wound healing.

Treatment

Therapy for mast cell disease is varied depending upon the histologic grade of disease, the clinical stage, and the availability of modalities such as radiation therapy. For the most part, **surgery** is still the mainstay of therapy for local mast cell disease. Surgery with 3-cm margins into normal tissue has been traditionally recommended and is often curative for lower grade lesions. Recently, researchers have questioned the need for such extensive margins, particularly in Grade I disease. The definition of what constitutes a "dirty margin" on histology is also subject to debate. Because mast cells normally reside in dermal tissues, it is possible that the pathologist may report normal mast cells at the margin of excised tissue. Unfortunately, there is no simple marker that can differentiate malignant from benign resident mast cells. Thus, more conservative surgical excision is being recommended by some authorities. However, in some cases, due to the size and/or location of the lesion, surgery may be incomplete. In these cases, wider surgical margins may be obtained, or radiation therapy for microscopic disease in the tumor bed may be recommended.

Radiation therapy for incomplete margins or for nonresectable disease has a high probability of success in controlling local MCT. In one study of 95 mast cell tumors treated on 85 dogs, 79% were free of tumor at one year and 77% were tumor free at 2 years. Another recent study of dogs that were radiated for incomplete surgical margins showed 96% tumor-free survival at 1 year and 88% tumor-free survival from 2 to 5 years after radiation. Palliative radiation of Grade III mast cell tumors resulted in complete remission with a median duration of 33 weeks or a partial remission with a median duration of 16 weeks (all subject to improvement in quality of life).

Chemotherapy may be reserved for dogs with nonresectable or metastatic lesions. The efficacy of chemotherapy in preventing recurrence or metastasis of mast cell tumor has not been documented. Glucocorticoids are commonly used in treatment of this disease. The combination of vinblastine and prednisone is commonly prescribed for the treatment of mast cell tumors. Intralesional triamcinolone (1 mg/cm of tumor) may also be helpful as palliation in cases where surgical resection is not pursued. CCNU (Lomustine) has been reported to induce responses in dogs with metastatic mast cell disease. However, the response to any of these agents may be unpredictable.

FELINE MAST CELL TUMORS

Mast cell tumors occur in the skin and in visceral sites in the cat. Skin tumors occur in older (mean age 9 years) cats, with no observed sex predilection. Siamese cats are three times more likely than other breeds to develop cutaneous mast cell tumors, which are histiocytic in appearance and prone to spontaneous regression. Visceral mast cell tumors tumors occur in the spleen, mediastinum, and nodes. There is no feline leukemia virus (FeLV) association. Cats also are prone to an aggressive intestinal form of mast cell tumor, which is associated with vomition, weight loss, diarrhea, and anorexia. Tumors in the intestine are composed of poorly differentiated cells. Most cutaneous mast cell tumors of cats are well differentiated and benign, but occasionally have been reported to metastasize and often appear as multiple lesions in the skin. Visceral mast cell tumors of the spleen may cause massive splenomegaly and vomiting due to gastrointestinal ulceration from histamine release. When visceral organs such as spleen and liver are involved, mastocythemia and bone marrow involvement may be detected on staging evaluation. Occasionally cats with visceral mast cell tumors will develop multiple metastatic foci in the skin. Mediastinal involvement presents like thymic lymphosarcoma, with dyspnea and pleural effusion. Cytology of the pleural fluid reveals mast cells and eosinophils.

Staging

Staging for mast cell tumors in cats involves a minimum database and buffy coat evaluation for occult mastocythemia, thoracic radiographs, and abdominal ultrasound with fine needle aspiration of involved organs.

Treatment

Treatment of dermal mast cell tumors is surgery, which occasionally must be multiple due to the tendency of cats to have multiple solitary tumors over long periods of time. Because these tumors are well differentiated in general, surgery is curative most often for solitary lesions. Corticosteroids (1 mg/kg/day prednisone) may be helpful. Radiation therapy can be useful for nonresectable or invasive tumors. Visceral mast cell tumors in cats are variable in behavior. Cats may present with massive splenomegaly, prompting the clinician to render a poor prognosis. However, splenectomy alone results in median survival times of 12 months, with some cats reported to live 3 years or more. Treatment of gastric and duodenal ulcers is symptomatic as described for canine mast cell tumors. Intestinal mast cell tumor carries the poorest prognosis of all of these presentations. Intestinal mast cell tumor often is associated with systemic involvement and patients are debilitated from malassimilation before diagnosis. If possible, bowel resection with 5 to 10 cm margins should be performed. Corticosteroids may be palliative for these cats, but most with intestinal involvement die within 4 months of diagnosis. Systemic chemotherapy has been attempted for cats with disseminated MCT. Agents such as used for the dogs may be tried. However, no reports of prolonged survival as a result of chemotherapy have been published.

AMPUTATION OR LIMB SALVAGE FOR OSTEOSARCOMA: WHAT'S BEST?

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AMPUTATION

For most dogs and cats, amputation is, by far, the easiest, least complicated, and most cost effective treatment to remove the primary tumor in cases of osteosarcoma. Amputation is a surgical technique most veterinarians are familiar with and it requires no specialized surgical equipment other than the standard surgical pack. For primary tumors involving the forelimb, a forequarter amputation is recommended. This method results in superior cosmetic results for most dogs. In addition, if the primary tumor is in the proximal humerus, forequarter amputation will provide for clean surgical margins, whereas disarticulation at the scapulo-humeral joint will result in residual local disease left in the patient. For hindlimb tumors, a coxofemoral disarticulation is preferred over a mid-femur osteotomy especially in cases where the tumor is in the distal femur. Removing the entire femur ameliorates the risk that the tumor has spread proximally within the marrow cavity where it is not apparent radiographically. In cases in which the tumor is located in the proximal femur (femoral neck), an acetabulectomy (without opening the coxofemoral joint) is recommended. This technique is similar to a partial hemipelvectomy where the entire coxofemoral joint including the acetabulum and associated joint capsule is removed *en bloc* with the limb. In cases of proximal femur osteosarcoma, coxofemoral disarticulation has resulted in a high rate of local recurrence.

Contrary to popular myth, large and giant breed dogs do quite well with amputation, even if there is existing degenerative joint disease. We very commonly perform amputations on large and giant breed dogs, as this is the patient population that is most likely to have osteosarcoma. Most owners are more comfortable with limb amputation in their pet if they understand that while larger dogs may take more time to adjust, they typically enjoy an excellent quality of life. When one compares the risk of long-term complications between limb-sparing surgery and amputation, amputation clearly comes out the winner. So, in comparison, when complications related to chemotherapy are set aside, dogs with amputations spend less time at the veterinarian's office and enjoy far fewer surgical complications than dogs undergoing limb-sparing surgery.

LIMB-SPARING TECHNIQUES

Limb sparing (limb salvage) is one of several alternatives to amputation. There are several limb-sparing techniques available. Nearly all (except intraoperative radiation) require that the tumor is located in the distal radius or mid-diaphyseal region within a long bone. Other sites have not been successfully salvaged and may be better candidates for palliative treatments if amputation is not possible. Other candidacy requirements for limb salvage are that there is no metastatic disease, no pathologic fracture, and no existing co-morbidities that would preclude the dog from living out the expected median survival time (eg, dilated cardiomyopathy [DCM], severe unregulated diabetes). It is important to inform the client that limb salvage procedures are nearly always more complicated than amputation and are considerably more expensive. At CSU, most techniques cost about $7000 for the surgery and immediate postoperative care. The cost of chemotherapy and follow-up visits with radiographs are additional.

Traditional Limb-Sparing Surgery Using Cortical Allografts

Traditional limb-sparing surgery involves a marginal resection of the involved tumor bone and replacement of the defect with a cortical allograft and stabilization with internal fixation. Arthrodesis of the adjacent joint is usually necessary, although in cases where the tumor is located in the mid diaphysis of a long bone, intercalary grafting is possible with excellent results. In our experience, distal radius and ulna sites result in the best function following limb spare. Arthrodesis of the carpus is well tolerated by dogs of most any size. With arthrodesis of the shoulder, stifle or tarsus, function ranges from very poor to good and the complication rate is considerably higher than distal radius or ulna sites, especially in larger dogs. For these reasons, we generally recommend amputation (for amputation candidates) for osteosarcoma in sites other than distal radius or ulna. Limb sparing should be questioned for dogs presented with metastatic disease due to the cost and commitment required for the procedure in light of a short-term survival outlook. Limb-sparing candidates are those that show radiographic tumor involvement of 50% or less of the involved bone. Involvement of both distal radius and ulna will not preclude a patient from limb sparing, but the complication rate can increase. In these cases a radial allograft is used, but the ulna is not grafted. Ulna lesions are generally treated by ulnectomy without allograft placement since the radius is the primary weight-bearing bone. Pathologic fractures increase the chances for soft tissue contamination with tumor cells locally and amputation should be considered.

For large tumors, especially those with large soft tissue components, preoperative downstaging of local disease can improve the success of the procedure as well as the ease of resection. Our work has demonstrated that approximately 30 Gy of radiation (traditionally in 10 3 Gy fractions) combined with cisplatin as a radiation sensitizer will result in 80% or better necrosis of the tumor. This degree of necrosis has been shown to significantly reduce local tumor recurrence. Higher radiation doses are required to obtain the same degree of necrosis if radiation is used alone; increasing the occurrence of radiation-related complications.

Complications following limb sparing include tumor recurrence, infection, and implant failure. Proper case selection is paramount. MRI of the affected leg is often helpful to determine the proximal extent of marrow involvement. These results are combined with the bone scan results and radiographs help determine the level of resection to ensure that no disease is left behind. Advanced imaging is very helpful; however, limb sparing requires that the plane of dissection is close to the tumor to ensure "sparing" of as much normal tissue as possible. Thus, local recurrence occurs more frequently with limb-salvage procedures than with amputation where large normal tissue margins are obtained. Local tumor recurrence can often be treated with a re-sparing procedure, especially if it occurs in the adjacent bone. As would be expected, success rates drop with successive local recurrence and salvage procedures. If further salvage is not feasible, amputation can be re-considered.

The most frequent complication seen (outside of osteosarcoma disease) following limb sparing is infection. An infection rate approaching 50% is common. This is due to multiple factors including extensive surgical field, large resection with compromise of arterial, venous and lymphatic flow, local and/or systemic chemotherapy with or without radiation, large allograft and metallic implants and lack of soft tissue covering (especially distal radius and ulna). Infection rate is high despite intraoperative and long-term postoperative antibiotic therapy. Many infections can be controlled with appropriate antibiotic therapy. A small percentage cannot be controlled and end in amputation. We have been able to improve our treatment success of severe infections with the surgical implantation of aminoglycoside antibiotic-impregnated polymethyl-methacrylate beads, presumably due to overcoming bacterial resistance.

As a result of the high infection rate, several new alternatives to allograft limb salvage have been explored. These procedures are briefly described below.

Bone Transport Osteogenesis

This technique utilizes circular external fixators to perform a procedure known as bone transport limb salvage. This method of limb salvage involves resection of the bone tumor followed by slow transportation of a nearby segment of bone into the defect. Using the principles of Ilizarov (the Russian physician credited with discovery of bone transport osteogenesis), the bone segment is slowly transported into the defect while new, autogenous bone forms in the trailing distraction pathway. The major advantage to bone transport limb salvage is that the new bone formed by this method is autologous tissue and has an excellent blood supply. Thus the newly bone is highly resistant to infection. Other advantages are the lack of a need for bone banking, donor animals, or internal fixation. In addition, animals are fully weight bearing during the transport process and after the initial surgery; the transport can be performed by the client at home. Its disadvantages are that it is relatively complicated to perform and requires that the patient wear an external fixator for a length of time sufficient to create the new bone. Despite some limitations, initial long-term results are very encouraging and current research is aimed at improving frame design and decreasing time of transport.

Intraoperative Radiation

A second technique (affectionately known as the "flip-n-nuke" technique) involves extremely high single doses of irradiation given to the affected bone at the time of surgery. This technique is aimed at killing all cells (normal and malignant) in the tumorous bone region while protecting normal soft tissues. The irradiated bone and tumor is reinserted and serves to perfectly reconstruct the defect. This technique involves osteotomy above or below the affected site and removal of soft tissues from the tumor bone. The neurovascular bundle is held away from the affected bone and the tumor is pivoted from the site on the intact joint tissues. A single dose of 70 Gy radiation is then directed to the tumor. The radiated bone is then anatomically replaced and fixed back into position using either an interlocking nail system or dynamic compression plating. The advantage to this technique is in the potential sparing of joint function and the potential use in non-distal radius sites. To date, two proximal humeral sites, one distal humeral site, one distal femur and one distal tibia have been treated. All patients have had at least good initial function. Long-term results have been less encouraging, however. Four patients have had to have implant revisions within 5 months of initial surgery, including one amputation. Local tumor recurrence has occurred in two patients and infection in two patients. Follow-up on this subset is relatively short and further evaluation as well as technique modification is indicated before this technique can be recommended routinely.

Ulna Autograft Technique

This limb-sparing method involves the use of the ipsilateral ulna as an autograft. Two techniques have been employed to use a vascularized ulna graft to reconstruct the distal radius defect. The vascular supply of the distal ulna graft is based upon the musculoperiosteal cuff formed by the pronator quadratus, abductor pollicus longus and ulnar head of the deep digital flexor muscles. The vascular supply is the caudal interosseous artery and vein. In one method, the ulna is pivoted on an intact vascular pedicle. In the other method, direct microvascular anastomosis is performed between the caudal interosseous artery and vein and the radial artery and vein. The microvascular anastomosis method is useful in cases where the tumor has invaded the distal aspect of the ipsilateral ulna, because portions of the proximal ulnar diaphysis may be used or, in some cases, the contralateral ulna.

Metal Endoprostheses

This limb-sparing method utilized a metal endoprosthesis in place of the traditional allograft. Initially, this method was developed in an attempt to decrease infection rates. While, early data suggests that there is only a modest, if any, decrease in infection, this technique is technically very simple and may allow limb-sparing procedures to become more widely available. In addition, endoprosthetic reconstructions may eventually be able to be combined with total arthroplasty techniques to allow better overall function and provide limb-sparing options for anatomic locations other than the distal radius to be considered.

OTHER OPTIONS

When limb sparing is not feasible there are additional alternatives other than amputation to consider. Palliative radiation therapy has excellent success at relieving pain. The protocol involves 3 to 4 treatments of radiation with various intervals between successive dosing and is fairly inexpensive compared with other treatments. Approximately 85% to 90% of dogs have an excellent response. Pain relief lasts for 3 to 4 months on average. We have some experience with adding chemotherapy to palliative radiation protocols. These patients have received various chemotherapy protocols including doxorubicin as a single agent, alternating doxorubicin and cisplatin (or carboplatin) and cisplatin (or carboplatin) as a single agent. We have observed survival times in the 8- to 9-month range in some animals, although these results are not consistent and prospective studies have not been performed.

AMPUTATION IN THE CANCER PATIENT: HELPING OWNERS DECIDE

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Amputation is often required for control of certain diseases or severe trauma. Owners almost uniformly have a negative reaction to the concept of amputation in dogs and cats. Many owners believe that amputation is a cruel and mutilating procedure. As health care professionals, veterinary technicians are often called upon to answer questions regarding amputation and are intimately involved with the postoperative management and discharge of these patients. Therefore, it is important for veterinarians and technicians to inform owners and dispel common myths associated with amputation in pets. In addition, appropriate client education prior to discharge can greatly add to the client's level of satisfaction in the first few days or weeks after a pet's amputation. Below are some common myths, questions and comments to which veterinarians and technicians may be asked to respond. Facts and specific helpful information for pet owners follow.

Myth: *Amputee pets have a poor quality of life.*
Fact: Most animals require an amputation to achieve long-term quality of life that would not be possible without an amputation. Dogs and cats with amputations are able to run and play, swim, exercise with their owners, work and enjoy life. It is helpful to keep a photo album or videotapes of amputees performing normal activities or playing and running. Owners will also be able to have an idea of how the patient will look after the hair returns and the incision is healed.

Myth: *If I concede to amputate my animal's limb, the other pets in the house will "pick on" or act aggressively toward the amputee.*
Fact: Although aggressive behavior on the part of another house pet is not unheard of, the change in appearance associated with amputation rarely causes aggression in and of itself. Thus, if the pets in the household were not normally aggressive toward one another, it would be rare for the amputee to suffer any extra aggression simply because of a missing limb.

Myth: *Large dogs do poorly with amputation.*
Fact: While smaller dogs and cats uniformly do extremely well with amputation, larger dogs also do very well as a rule. At our institution, the vast majority of amputations are performed on large breed dogs for treatment of osteosarcoma. It is the exception, and not the rule, that a large or giant breed dog will have significant difficulty after amputation. Most large breed dogs are able to negotiate stairs and so forth with no problem. Occasionally a dog will require help going down the stairs. Severely obese large breed dogs may need support with a towel until a reasonable amount of weight loss is achieved. Obviously severe generalized neurological deficits would be a contraindication for amputation. In many cases, dogs are already walking on three legs immediately prior to amputation because of the pain or dysfunction associated with the disease. This is helpful to point out to owners, if present.

Myth: *The pain associated with amputation is excessive and a pet animal will suffer severely in the immediate postoperative period.*
Fact: Amputation performed without pain management in the postoperative period would certainly be painful. However, with appropriate pain management, patients can be kept very comfortable. Suggestions for effective pain management in the immediate postoperative period would include preemptive analgesia with fentanyl transdermal patches and opioids in the preanesthetic medications, continuous rate intravenous infusion of opioids with or without the addition of ketamine postoperatively, the use of epidural analgesia and so on. These techniques are very effective and can be continued for 48 hours or more. The addition of nonsteroidal anti-inflammatory agents such as carprofen in the postoperative period is often sufficient after the second postoperative day.

SUGGESTED DISCHARGE PROTOCOL FOR AMPUTEES

Owners are often very apprehensive about seeing their pet after amputation. Below are some ideas that have worked very well in our institution and have improved client satisfaction with the procedure.

- Before the client comes to pick up the pet, ask the owner to bring a clean, large (old) t-shirt.
- Bring the client into an exam room away from the traffic flow and speak with them *before* bringing in the pet.
- For some reason, owners commonly seem to be shocked at the amount of hair that has been clipped for an amputation. Remind owners that a large area of the body has been clipped for surgery.
- Remind owners that the incision will appear large and bruised. Bruising usually gets worse over the 3 to 4 days following surgery and then begins to get better. This is normal.
- Inform owners that mild swelling is also normal but liquid discharge of any kind or large fluctuant swellings should be checked by the veterinarian.
- Cold compresses using ice packs covered with towels in the first 2 to 3 days after returning home is helpful to reduce swelling and discomfort. After this time, warm compresses are better.
- Larger dogs may have initial trouble on slick floors. Keep the pet on non-slip surfaces and use a towel to "sling" and support the animal going up and down stairs until the pet learns to negotiate these on his/her own.
- Large dogs may prefer to eat standing up from an elevated food dish at first (this is especially true for front limb amputations).

- Inform the owners that the animals will require time to recover fully. For the first 2 weeks following amputation, it is common for the pet to sleep and be less active. This is normal and should be encouraged; however, there should be steady improvement. Any setback should generate a phone conversation.
- Prior to reuniting the owner with the pet, place the T-shirt (from the owner) on the pet so that it covers the incision. Some technicians use a stockingette "sweater" which also works nicely. This allows the owner to have a moment to greet the pet before reacting to the incision. When the owner is ready, show them the surgery site explaining the bruising again and the sutures. Often owners will comment that it looks better than they thought it would look.Indicate that they should check it daily for signs of infection, etc.
- We find that owners greatly appreciate a phone call in the first 48 hours after discharge and usually have many questions or concerns that can be addressed by the technician.

The above information represents an overview of a protocol that we have used successfully for the last 15 years. Technicians are a key part of the case management team at our hospital and can ensure quality interactions with the client simply by keeping them informed and using good communication skills. Although the initial response to the need for an amputation is often negative, most clients indicate a high level of satisfaction with the procedure when owner education and communication is well managed.

SOFT TISSUE SARCOMAS: YOUR QUESTIONS ANSWERED

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The soft tissue sarcomas are a group of tumors with differing morphologic features that share similar biologic behaviors. They occur in both humans and animals and include a variety of tumor types. These tumors arise from a variety of non-bone connective tissues and may originate in visceral and non-visceral sites. Soft tissue sarcomas constitute approximately 15% of all skin and subcutaneous tumors in the dog and approximately 7% of all feline skin and subcutaneous tumors. Incidence estimates for canine and feline soft tissue sarcomas arising from visceral sites are less accurate.

Nomenclature given to tumors that are grouped under the soft tissue sarcoma heading include fibrosarcoma, hemangiopericytoma, liposarcoma, rhabdomyosarcoma, leiomyosarcoma, malignant fibrous histiocytoma, malignant nerve sheath tumors (neurofibrosarcoma, schwannoma), myxosarcoma, myxofibrosarcoma, mesenchymoma, and spindle cell tumor. These tumors differ in histologic appearance to various extents and are named after the connective (mesenchymal) tissue from which they are presumed to arise (see Table 1). Despite differing histologic features, soft tissue sarcomas are grouped together because of some important features of biologic behavior that are common to all the soft tissue sarcoma tumors. These features have been described by Withrow and MacEwan and include:

1. An ability to arise from any anatomic site in the body
2. The propensity to appear as pseudoencapsulated tumors with poorly defined histologic margins
3. A tendency to infiltrate through fascial planes
4. Common local recurrence after conservative excision
5. Metastasis through hematogenous routes
6. A poor response to chemotherapy and radiation therapy in cases where gross tumor is present[1-3]

In general, these tumors share a low to moderate metastatic rate and are locally invasive. Other tumors of connective tissue origin such as osteosarcoma, chondrosarcoma, hemangiosarcoma, lymphangiosarcoma, and synovial cell sarcoma are not usually considered under the soft tissue sarcoma heading because of the relatively higher metastatic rate associated with these tumor types.[1,2] Thus, not all tumors with the "-sarcoma" suffix are included in the soft tissue sarcoma grouping (see Table 1).

Signalment

The median age for dogs affected with soft tissue sarcomas is 10 years with a range from 6 months to 17 years. Although some reviews have suggested a female predisposition, others have not. Commonly affected breeds include boxers, German Shepherds, golden retrievers and Doberman pinschers. Most every breed has been reported, but large breeds seem to be affected more commonly than toy and small breeds

Clinical Signs

Most dogs present with large firm painless swellings, although dogs with nerve root tumors may be exquisitely painful. Tumors of the extremities are typically not associated with lameness, although some dogs with large tumors may demonstrate functional lameness. Subcutaneous sites are most common, and any anatomic site can be affected.

Physical Examination Findings

Most dogs have firm painless swelling of the affected region. There may be functional impairment due physical presence of the tumor. Dogs with oral tumors may be dysphagic.

Clinical Work-up

When a soft tissue sarcoma is suspected, fine needle aspiration should be performed, results may be suggestive of mesenchymal neoplasia, but will rarely be diagnostic. Thoracic radiographs should be performed because, although clinically evident metastasis at the time of diagnosis is rare, its discovery imparts a poorer prognosis. Regional lymph nodes should be evaluated and aspirated if they are enlarged. Lymph node metastasis of soft tissue sarcomas is less common than lung metastasis, but is not rare. Incisional biopsy of soft tissue sarcomas should always be performed prior to

Table 1. Soft Tissue Sarcomas (Low to Moderate Metastatic Rate[1])

Low metastatic rate
- malignant fibrous histiocytoma
- malignant nerve sheath tumor
- hemangiopericytoma
- leiomyosarcoma
- mesenchymoma

Low to moderate metastatic rate
- fibrosarcoma
- myxosarcoma
- rhabdomyosarcoma
- spindle cell tumor
- liposarcoma

Other mesenchymal tumors (high metastatic rate, NOT included under soft tissue sarcoma)
- hemangiosarcoma
- osteosarcoma
- chondrosarcoma
- synovial cell sarcoma*
- lymphangiosarcoma

*Sometimes grouped under the soft tissue sarcoma heading definitive surgical excision to determine histological type and grade because these help determine prognosis as well as the extent of surgical excision required to achieve clean surgical margins.

Treatment

The mainstay of treatment of soft tissue sarcomas is wide local surgical excision. Surgical margins should be at least 2 cm away from any visible or palpable tumor. With grade III tumors, margins >3 cm may be required to achieve clean margins. Careful consideration of regional anatomy and options for closure should be made prior to surgery. A three-dimensional sphere at the required distance needs to be visualized, and completely excised without regard for surgical closure. Again, the time to consider anatomy at risk and options for surgical closure is before the patient enters the surgical suite. Decisions made under duress during surgery with fears of inability to close frequently lead to malignant cells being left in the patient. Skin grafts and flaps requiring extensive dissection of adjacent tissues should be used with discretion for fear of contaminating large amounts of tissue if surgical margins are incomplete. One option is to leave wounds that cannot be closed with native tissues open to heal by second intention, or to be closed primarily using plastic procedures once surgical margins have been determined to be clean. Surgical margins should be inked and evaluated by a veterinary pathologist. All samples must be submitted for histopathologic evaluation. If margins are found to be incomplete, a second surgery can be performed, where the entire surgical scar is treated as a new tumor and 2-cm margins in all directions are taken. Radiation therapy offers an excellent choice for “cleanup” of incomplete excision of soft tissue sarcomas.

Chemotherapy

Chemotherapy is not routinely indicated in most soft tissue sarcomas. The exceptions to this rule are grade III (high grade) sarcomas. A significantly higher metastatic rate is seen with grade III tumors and as such, adjuvant chemotherapy is indicated to delay or prevent metastasis. Most protocols involve single-agent doxorubicin or combinations therapies including doxorubicin.

Prognosis

Factors which are prognostic include tumor grade, with high-grade tumors having significantly more local recurrence, metastasis, and tumor-related death; patient age, where patients under 1 year of age almost always have high-grade tumors; anatomic location, where tumors of the extremities, below the knee or elbow, almost never metastasize and tumors of the oral cavity have a somewhat higher metastatic rate; the presence of grossly evident metastasis at the time of diagnosis, which imparts a grave prognosis; and the completeness of surgical margins, which is highly prognostic for local recurrence. The median survival time for patients having only aggressive surgical treatment of soft tissue sarcomas is 1400 days. The one-year local control rate for aggressive surgery and for aggressive surgery with adjuvant radiation therapy for incomplete surgical excision is approximately 90%.

ADJUVANT RADIATION THERAPY FOR SOFT TISSUE SARCOMAS

For circumstances where surgery alone cannot ensure complete removal of a soft tissue sarcoma, adjuvant radiation therapy is used. Radiation therapy for soft tissue sarcomas becomes necessary when complete resection is impossible or when the owner refuses the surgical procedure necessary for complete resection. For example, many owners choose marginal resection followed or proceeded by radiotherapy for residual disease rather than amputation (or other aggressive excision) for a pet with a soft tissue sarcoma of an extremity, even though amputation is almost certainly a curative procedure. Because we are dealing often times with soft tissue sarcomas of low metastatic potential (exception is the high-grade sarcomas, which have a 40% to 60% chance of metastasis), a decision for amputation can usually be made later if radiotherapy fails.

With the advent of routine use of megavoltage radiation in veterinary medicine and appreciation of aggressive time-dose fractionation schemes, successful local control of soft tissue sarcomas has been possible. A recent study documented 21 dogs with incompletely resected sarcomas treated with cobalt radiation. The total dose of 63 Gy given in 3 Gy fractions over 7 weeks resulted in 1 and 2 year control rates of 95% and 75%, respectively.

Although radiation therapy is most often given postoperatively in veterinary medicine, some centers are trying to use preoperative radiation therapy for the locally aggressive feline vaccine-associated sarcomas. In 1994, preliminary results from North Carolina State University (NCSU) reported median progression free intervals of 137 days and 280 days for radiation therapy alone versus preoperative radiation therapy, respectively, for cats with vaccine-related fibrosarcomas. Cronin et al published the results on 33 cats treated at NCSU with preoperative radiation therapy. The median disease-free interval and overall survival were 398 and 600 days, respectively. There were 19 treatment failures: 11 cats had only local recurrence, 4 cats developed metastatic disease, 4 cats had local recurrence and metastasis. The presence of tumor cells at the margin of resected tissue after radiation was the only variable that influenced treatment success. The median disease free interval in cats with dirty tumor margins was 112 days versus 700 days for 26 cats with clean tumor margins ($P<0.0001$). Approximately 40% of the cats with clean margins were alive at 3 years.

Although the optimal combination of radiation therapy and surgery is not known, the above results suggest that many soft tissue sarcomas that are not or cannot be completely excised can be controlled for a significant amount of time with the multimodality approach of surgery and radiation therapy. With more frequent use of the grading system for soft tissue sarcomas, more complete information about risk of metastasis and long-term prognosis may help owners make the best decision about their treatment options.

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TUMORS OF THE SPLEEN AND LIVER: YOUR QUESTIONS ANSWERED

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HEPATOBILIARY CANCER IN DOGS AND CATS

The most common primary hepatic tumors in dogs are hepatocellular adenoma and hepatocellular adenocarcinoma. The most common malignant hepatic cancers of cats are hepatocellular carcinoma and cholangiocarcinoma. Most animals with hepatobiliary neoplasia are older than 10 years. Clinical signs are often nonspecific but include the presence of an abdominal mass, weight loss, vomiting, ascites, and occasionally icterus. Icterus is relatively uncommon sign in dogs unless there is obstruction of the biliary outflow tract. In cats however, icterus is a common presenting clinical sign associated with hepatic tumors.

Initial workup should include blood work (including clotting profiles), urinalysis, and three-view thoracic radiographs, and an abdominal ultrasound should be performed. Fine-needle aspiration (FNA) of the mass can safely be performed using ultrasound guidance and may help the clinician determine the disease process. Advanced imaging such as CT scan or MRI can be helpful for extremely large tumors or those in deep-chest breeds to help determine the likelihood of successful excision. Serum alanine aminotrasnferase (ALT) and alkaline phosphatase (ALP) are often elevated in dogs and cats with hepatic tumors.

Early and aggressive excision is the treatment of choice for most hepatobiliary masses. The presence of diffuse involvement in multiple liver lobes can preclude complete surgical excision. On occasion, surgical cytoreduction can provide palliation of clinical signs and a better opportunity for adjuvant chemotherapy to have a positive effect. Most hepatobiliary tumors are slow growing and tend to push normal parenchyma out of the way, allowing for excision of even very large masses. Up to 80% of the functional liver can be removed without long-term functional deficits. In most cases, however, the tumor volume does not represent normal functioning liver, and this again lends to the ability to remove large solitary masses with little or no residual function deficit. Blood transfusions are often necessary during surgery of the liver. Stapling equipment (eg, TA staplers, GIA) allow rapid excision of solitary tumors.

Hepatocellular Adenocarcinoma

Hepatocellular carcinomas occur in one of three forms. The first form is characterized by a single large mass, usually pedunculated. This form is sometimes termed the *massive form* of hepatocellular adenocarcinoma. These are easily amenable to excision via lobectomy or partial hepatectomy. The second form, known as the *nodular form*, is represented by infiltration of varying sized masses in all liver lobes. The third form is known as the *diffuse form* and is characterized by diffuse enlargement due to infiltration by non-encapulated, invading neoplastic tissue. The second two forms are not amenable to excision in most cases. Metastasis is common both to the liver and to distant organs such as the lungs in all the forms. In cases of solitary tumors, long remissions have been reported in animals that have had complete excision. Unfortunately, little has been published on the efficacy of chemotherapy for treatment of hepatic tumors in dogs and cats. In humans, primary liver tumors are thought to be relatively chemotherapy resistant.

Hepatocellular Adenoma

These are the benign counterparts to the hepatocellular adenocarcinomas. Adenomas of the liver can become very large prior to clinical detection and may cause abdominal effusion. They are usually clearly demarcated from normal liver and are most commonly single masses. They can be difficult to grossly differentiate from the massive form of hepatocellular adenocarcinoma but on histology they are quite benign. They do not metastasize; therefore complete excision is curative.

Cholangiocarcinoma (Biliary Carcinoma)

These tumors develop from intrahepatic or extrahepatic bile duct epithelial tissue. This tumor is more common in cats than in dogs. Cholangiocarcinoma is widely metastatic to local lymph nodes and the peritoneum resulting in effusions. It is estimated that metastasis occurs in about 87% of dogs and 78% of cats.

SPLENIC TUMORS IN DOGS AND CATS

Hemangiosarcoma

Hemangiosarcoma is a malignant cancer of the blood vessel endothelial cells. It is the most common malignant tumor of the spleen. German shepherd dogs are known to be predisposed but the tumor occurs in other large breeds as well. Benign splenic tumors are also common, thus it is important not to presume all splenic tumors are hemangiosarcoma. Hemangiosarcoma can occur in any organ but is most frequently diagnosed in the spleen of dogs. Other primary sites include the right atrium, skin and subcutaneous tissue. It is uncommon in cats.

Splenic hemangiosarcoma is usually manifested by clinical signs of weakness, pallor, and collapse. Another common presenting scenario is a history of episodic weakness followed by recovery within 12 to 24 hours. The waxing and waning weakness followed by recovery is usually due to hemorrhage and subsequent autotransfusion of free abdominal blood (hemoperitoneum). Hemoperitoneum can be diagnosed via abdominocentesis. The finding of large amounts of free abdominal blood in an older, large breed dog, with the concurrent findings of weakness and anemia on presentation, should be considered consistent with a ruptured splenic tumor. In the absence of a palpable abdominal mass, an important diagnostic differential is rodenticide toxicity and the owners should be questioned carefully to determine if the patient might have been exposed. Depending on the timing of presentation relative to the hemorrhage, the abdominal effusion may have been completely reabsorbed or a serosanguinous effusion may be present. Changes in red blood cell morphology such as acanthocytes, schistocytes, and nucleated red blood cells are commonly noted on the complete blood count in animals with hemangiosarcoma. Shistocytes are associated with red cell fragmentation and microangiopathy. The presence of these morphology changes on the complete blood count (CBC) should increase the clinician's index of suspicion for hemangiosarcoma.

Ventricular arrhythmias are a common finding in dogs with splenic tumors, especially in those that have ruptured and bled. These are most likely due to either myocardial hypoxia associated with severe anemia, or to myocardial depressant factors released by the tumor. Ventricular tachycardia can be present at the time of surgery but is commonly seen within 12 to 36 hours after surgery. Often, supportive management such as fluid therapy and correction of electrolyte imbalances will be sufficient support for the patient; however, in certain instances; the arrhythmias should be addressed medically. If the arrhythmias 1) interfere with cardiac output as evidenced by poor peripheral pulses or collapse, 2) are multiform, 3) have subsequent premature beats inscribed on the wave of the previous complex (R on T phenomenon) or 4) have a sustained ventricular rate of greater than 180 beats per minute, anti-arrhythmic drugs are indicated. Lidocaine given intravenously (IV) at 2 mg/kg bolus followed by a continuous rate infusion (CRI) of 50 µg/kg/min is effective in many patients. The CRI can be increased to 75 µg/kg/min if lower doses are ineffective. Procainamide 10–15 mg/kg IM or PO can be used when the animal is more stable. Procainamide at 10–15 mg/kg given IV as a slow bolus can be used if the arrhythmias do not respond to lidocaine therapy; however, severe hypotension can result. Up to 25% of dogs with splenic hemangiosarcoma may concurrently have right atrial hemangiosarcoma; therefore it is important to examine the right atrial appendage with ultrasonography for the presence of a mass. Metastasis to the lungs can be noted, emphasizing the importance of a complete staging workup.

A common benign mass, splenic hematoma, may also rupture and bleed into the abdomen and is an important differential diagnosis for hemangiosarcoma. Collapse, hemoperitoneum and anorexia are common signs with both conditions. Both are treated with splenectomy; however, the prognosis is drastically different and therefore it is important to distinguish between the two diseases.

Ruptured splenic tumors should be considered a surgical emergency. Animals presenting with an abdominal mass, collapse, pallor, and hemoperitoneum should be treated for shock, given a transfusion of packed cells or whole blood and taken to surgery when stable. Although, some clinicians prefer to stabilize overnight, I find that a significant proportion of these patients are in disseminated intravascular coagulation (DIC) and are at risk for fulminant, lethal hemorrhage. Removal of the primary tumor is the best treatment to prevent or address DIC and many animals rapidly stabilize after surgery.

Treatment for splenic hemangiosarcoma is splenectomy followed by adjuvant chemotherapy. Splenectomy will relieve abdominal distention caused by the tumor and halt bleeding. It is very important to realize that one cannot distinguish between benign and malignant tumors of the spleen by gross examination. Similarly, the surgeon should avoid assuming that any lesions seen in the liver at the time of surgery are definitive metastases. Nodular hyperplasia may appear similar to metastatic disease; therefore, a liver biopsy is always indicated. The important message here is *never euthanize a patient suspected of having primary splenic hemangiosarcoma without histopathologic confirmation*, even if it appears that metastatic disease is present in the liver. Many clinicians have been grieved to find at necropsy that the primary splenic tumor was a benign hematoma and the nodules in the liver that were thought to be metastatic foci were nodular hyperplasia.

Splenectomy alone does not result in prolonged survival in patients with hemangiosarcoma as the tumor readily metastasizes to the liver and peritoneal cavity. Adjuvant chemotherapy is recommended for dogs with hemangiosarcoma and significantly improves survival time. At the University of Illinois we are using doxorubicin (30 mg/m^2) in combination with dacarbazine (DTIC) at 200 mg/m^2 for dogs with hemangiosarcoma. Median survival is approximately 10 to 14 months with this protocol however this data is still maturing

Other Splenic Tumors

Other splenic tumors seen in dogs and cats include lymphoma, leiomyoma, leiomyosarcoma, mast cell tumors, hemangioma and malignant fibrous histiocytoma. Leiomyoma and hemangioma are benign tumors. Splenectomy is curative. Leiomyosarcomas and malignant histiocytoma are in the soft tissue sarcoma family and have the potential to metastasize. Little is published on long-term survival of patients with soft tissue sarcomas of the spleen but it is thought that they are slow to metastasize. Therefore, early detection and splenectomy can be curative in some cases. Chemotherapy is given if metastatic disease is documented.

WHAT TO DO ABOUT NASAL TUMORS

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Intranasal tumors are reported to account for 1% to 2% of all tumors in dogs making them relatively uncommon tumors. These tumors can arise from within the nasal cavity itself or from within the paranasal sinuses. In addition, tumors can arise from the oral cavity, the nasal planum or the ocular orbit and can subsequently extend into the nasal cavity. Tumors arising from locations other than the nasal cavity or sinuses, except for nasal planum squamous cell carcinomas in the dog are not covered in this session. The vast majority of nasal tumors are malignant with reports indicating that only 10% to 20% of all nasal cavity tumors are benign in nature. Generally, nasal tumors are locally invasive and often only metastasize late in the course of the disease. At the time of diagnosis, the metastatic rate is reported as being less than 10%. In one necropsy study however, the metastatic rate increased to nearly 50%, with the most common sites of metastasis being the regional lymph nodes and lungs.

Some reports have found a higher incidence of nasal tumors in males, with the male to female ratio being from 1.3:1 to 3:1 depending on the study; while still other studies found no sex predilection. One theory for this is that urine marking and sniffing in the dog's territory could cause an increased exposure to environmental carcinogens.

Mixed breed dogs appear to have a similar incidence of intranasal tumors as purebred animals. There are certain breed predilections, however. Dolichocephalic breeds including collies and shelties have an increased incidence of nasal tumors, while brachycephalic breeds are often under represented in studies. One theory that accounts for these differences is based on anatomy. Brachycephalic breeds have a decreased surface area in their nasal passages and often mouth breath leading to decreased exposure of the nasal cavity to environmental carcinogens. On the other hand dolichocephalic breeds have an increased surface area in the nasal passages and nasal turbinates (that act as a filter) leading to increased carcinogen exposure.

Studies looking at environmental exposure to carcinogens as a cause for nasal tumors have been conflicting in nature. One study found an increased risk of nasal tumors in dogs that had a history of exposure to tobacco smoke while another did not. Another study found exposure to kerosene and coal heaters to be a risk factor. Still another found no increased incidence of nasal tumors for those dogs living in cities or within one mile of a factory. All of these studies suffer from having small numbers of patients enrolled (low power); meaning much larger numbers of dogs would be needed to expect to find differences between the groups.

CLINICAL SIGNS

Clinical signs are often nonspecific, resulting from destruction of normal structures. Clinical signs are present on average for 3 months with the range from 1 to 36 months before a diagnosis is made. Subsequently, nasal tumors are often advanced by the time that they are diagnosed.

Clinical signs of nasal tumors include epistaxis, nasal discharge (bloody, mucoid or mucopurulent), sneezing, respiratory stridor, neurologic signs and facial deformity. These signs can be unilateral or bilateral depending on the extent of the tumor.

The location of tumor within the nasal cavity affects the signs seen. For example if the tumor extends through the cribriform plate into the brain, the presenting signs can include seizures, neurologic deficits or behavioral changes. If the tumor extends through the orbit, ocular changes may be seen including exophthalmos, enophthalmos and ocular discharge.

DIFFERENTIAL DIAGNOSIS

As mentioned above the clinical signs of nasal tumors are often nonspecific. Facial deformity can be caused by a tooth root abscess. Nasal discharge can be caused by fungal infections with aspergillosis, allergic disease, foreign bodies such as foxtails, or parasites such as nasal mites. Epistaxis can be caused by foreign bodies, thrombocytopenia, hypertension, fungal infections, or bleeding disorders. What is important to note, however, is that primary bacterial rhinitis is rare in the dog and is should generally not be considered on your primary list of differentials for nasal discharge.

DIAGNOSIS AND STAGING

The initial workup for a patient suspected of having a nasal tumor includes a physical exam assessing for ocular and nasal discharge. The nasal passages should be assessed individually for airflow, the eyes retropulsed, local lymph nodes should be assessed for size and firmness, and the patient should be thoroughly ausculted.

A complete blood count (CBC), chemistry panel, and urinalysis should be obtained to evaluate the overall health of the patient and to help rule out other differentials as to the cause of the clinical signs. If neurological signs alone are present, a cerebrospinal fluid (CSF) tap may be indicated. If excessive bleeding is present, a clotting panel (including a prothrombin time [PT] and partial thromboplastin time [PTT]) should be obtained before performing a biopsy.

Thoracic radiographs should be taken to help rule out pulmonary metastasis, although studies indicate pulmonary metastasis occurs in only 3% to 10% of patients with nasal tumors at the time of diagnosis. Local lymph nodes should be examined and aspirated, particularly those that are firm, fixed in place or enlarged.

The nasal cavity and sinuses also need to be imaged. Nasal radiographs can be used, although they are less sensitive and specific than a CT scan. Changes seen on nasal radiographs include increased opacity in the nasal cavity or sinuses, turbinate destruction, deformation or loss of the nasal septum and cribriform plate destruction. The increased opacity seen on nasal radiographs can be difficult to interpret as mucous or blood in the nasal cavity or sinuses will look the same as a soft tissue mass. Bone destruction will also have to be extensive in order for it to be seen on plain radiographs.

CT scans provide a much more sensitive means for evaluation of the nasal cavity. Small areas of bony destruction including those in the cribriform are easily identified on CT if thin slices are obtained. The hard palate can also be evaluated which is important as its destruction and subsequent treatment can lead to oral nasal fistulas. Also, the submandibular and retropharyngeal lymph nodes can be evaluated on a CT scan, looking for asymmetry, enlargement and contrast enhancement filling defects.

A biopsy of the tumor is required for definitive diagnosis. There are multiple techniques for obtaining a biopsy. The best and easiest technique often depends upon the location of the tumor. Nasal tumor biopsies can be difficult often resulting in nondiagnostic samples. Small sized biopsy samples may only sample peritumoral inflammation, but larger samples carry a higher risk of complication (excessive hemorrhage). If the tumor is rostral it can sometimes be visualized using an otoscope cone and light source and can then be biopsied using alligator or pituitary cup forceps. Biopsies can be taken blindly but care should be taken not to place any instruments in further than the medial canthus of the eye so as not to penetrate the cribriform plate. A large bore plastic cannula placed on the end of a syringe can also be used for taking a blind biopsy. Rhinoscopy can be used to visualize and biopsy a nasal cavity tumor with the advantage of being able to visualize the area to be biopsied increasing the chance of obtaining a diagnostic sample. If there is facial deformity a punch biopsy sample can be taken. This can be helpful in those tumors arising from the frontal sinuses that break through the bone. Nasal flushes can sometimes yield pieces of tissue that can then be turned in for histopathology. Nasal flushes for cytology can sometimes be helpful in obtaining a diagnosis in cases of lymphoma, but with other tumor types this technique usually does not yield a diagnostic sample.

After a biopsy is taken the nasal cavity can be packed to help control bleeding. Several drops of phenylepherine (nasal spray) can be placed in the nasal cavity to help control bleeding. In severe cases of hemorrhage, epinepherine can be placed in the nasal cavity. Some bleeding over the next 1 to 2 days can be expected post biopsy.

Histopathology

The most common histologic types of nasal tumors are carcinomas (adenocarcinoma, carcinoma, transitional cell carcinoma, squamous cell carcinoma, and undifferentiated carcinoma), sarcomas (chondrosarcoma, osteosarcoma, undifferentiated sarcoma, and fibrosarcoma) and uncommonly mast cell tumors, transmissible venereal tumors (TVT), or lymphoma.

Prognostic Factors

Reported prognostic factors for intranasal tumors in the dog include facial deformity, destruction of the cribriform plate, lymph node involvement and the tumor crossing midline on imaging studies. Sarcomas in dogs are also thought to have a better prognosis with treatment than carcinomas.

Treatment Options

The median survival time for dogs with intranasal tumors without treatment is reported at 3 to 6 months. Palliative care includes antibiotics to treat secondary bacterial infections. If excessive epistaxis is present then ligation of one or both carotid arteries can sometimes provide relief without compromise to the patient.

Chemotherapy has only been used in a small number of cases of nasal carcinomas and sarcomas and is difficult to evaluate. There are reports of dogs receiving cisplatin with a 27% overall response rate and a median survival of 20 weeks. In one small study with 8 dogs, the use of alternating carboplatin, doxorubicin, and piroxicam at standard doses resulted in a response in the majority of dogs. Chemotherapy with vincristine can be curative for transmissible venereal tumors, requiring only several doses for a complete response in most cases. Reports of treatment of nasal tumors with immunotherapy and cryotherapy have not shown an advantage over no therapy alone.

Surgery alone has not been shown to increase survival times for malignant tumors. Rhinotomy procedures are invasive and have a substantial degree of morbidity and mortality associated with them. For these reasons surgery alone is not considered to be an effective treatment for intranasal or sinus neoplasia. Surgery can be used, however, to debulk a tumor before treatment with orthovoltage radiation.

Orthovoltage radiation therapy is a form of low energy radiation. Due to the poor penetration of this type of radiation, rhinotomy is required before attempting treatment. Because there is no skin sparing effect these patients tend to have high rates of morbidity associated with this treatment. As much of this type of radiation is absorbed in the bone late effects seen can include bone necrosis and subsequent fistula formation. Median survival times reported for orthovoltage radiation therapy are thought to be similar to those for megavoltage radiation therapy (see below).

Megavoltage irradiation of nasal tumors is the most commonly used method of treatment. Megavoltage radiation therapy is delivered by either linear accelerators or cobalt units with an energy of greater than 1 million electron volts. These machines also have the advantage of delivering the maximum amount of radiation below the surface of the skin (skin sparing effect). They also allow for better dosimetry and computer planning, allowing for less normal tissue to be irradiated and less side effects.

Median and mean survival with radiation therapy range from 8 to 25 months in different reports. We generally quote 8- to 12-month median survivals for dogs with carcinomas and 12- to 18-month median survival in dogs with sarcomas. In the literature the 1-year survival rates range from 20% to 81% and the 2-year survival rates range from 10% to 48%. Dogs with nasal planum squamous cell carcinoma have median survival of 2 to 3 months with treatment. Due to the poor prognosis treatment is generally not recommended with current dosing protocols.

Side effects from radiation therapy can be broken down into acute and late effects. Since radiation therapy is a localized therapy only the tissues in the radiation field are affected and depend upon the particular set-up for each patient. If one or both eyes are included in the field the patient should be monitored acutely for a corneal ulcer and long term for the development of keratoconjunctivitis sicca (KCS) and cataract formation. Rhinitis and mucositis in the oral cavity are also common side effects of radiation therapy. Usually these signs begin in the third week of therapy and resolve within several weeks of completion of therapy. Hair loss is common in the radiation field. Generally the hair will grow back, but new hair growth will be gray or white. The hair may also grow in thinner than normal.

It must also be remembered that the initial clinical signs seen by the owners may not resolve, depending on the amount of normal tissue destruction and nasal discharge and sneezing may continue.

References are available from the author upon request.

WHAT CAN I TREAT WITH RADIATION THERAPY?

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Radiation therapy (RT) is becoming an increasingly important part of cancer patient management in veterinary medicine. This article will cover the more commonly used types of RT including external beam radiotherapy and plesiotherapy, which is a type of brachytherapy. Traditionally, external beam RT is thought of as a local therapy, meaning that it is best used to treat the primary tumor and not systemic disease. It is most effective when used against microscopic disease after a tumor has been incompletely excised (postoperative RT) or when used against gross disease with a surgery scheduled to follow (preoperative RT). It is often used in combination with other therapies such as chemotherapy when there is risk of metastasis. There are circumstances, however, where it can be used as the only therapy (eg, nasal tumors), as a systemic therapy (eg, half-body RT for lymphoma), or as a palliative measure (eg, bone tumors).

MACHINES USED TO DELIVER RADIATION THERAPY

There are three main different types of machines used to deliver RT: orthovoltage machines, cobalt-60 machines, and linear accelerators. Orthovoltage machines are not widely used anymore and have the disadvantages of increased skin reactions, no computerized treatment planning systems, small field sizes, and high absorption of dose to bone. Cobalt-60 machines are still in use in veterinary medicine but also have some disadvantages compared to linear accelerators, which include increased penumbra at the field edge (leading to larger treatment fields), lower energy (leading to increased skin dosing) and less penetration of dose. Linear accelerators are becoming more widely used in veterinary radiation oncology and are the standard of care in treating humans. They are able to deliver a variety of energies and many of the newer machines allow treatment with either photons or electrons. Electrons allow the treatment of tumors over critical structures such as the intestine or GI tract without giving substantial dose to these organs. Linear accelerators also allow the use of smaller field sizes than cobalt units and allow a more homogenous dose to be delivered to deep-seated tumors.

HOW RADIATION IS DOSED

The basic unit of absorbed dose is the Gray (Gy). The older unit is the rad. When considering what total dose is going to be given several things need to be taken into account; Specifically: The radiosensitivity of the tumor, the dose delivered in each fraction, the time between fractions, the total number of fractions, the goal of therapy (palliative vs. definitive) and often most importantly the tolerance of the surrounding normal tissues.

While it is possible to kill any tumor cell with radiation, it is not possible to cure or even effectively treat every patient. The limiting factor in our ability to deliver a high and curative dose to a tumor is the effects on the irradiated surrounding normal tissues. Of course large doses of radiation delivered once weekly is more convenient and cheaper than small doses delivered daily, but you are less likely to get long-term control of a tumor and more likely to experience late side effects with coarse or hypofractionated protocols. Late side effects are generally the type that are most severe and can impact quality of life or even become life threatening. The smaller the dose given in each fraction the higher the total dose that can be delivered. Therefore, for patients who are expected to have medium or long-term survival, smaller dose per fraction protocols are the most appropriate. Three Gy delivered at each treatment (fraction) is the most commonly accepted dose used in veterinary medicine for definitive treatment of tumors that are not located in the brain for a total dose of 48–57 Gy. For brain tumors, many radiation oncologists use even lower doses per fraction protocols (2–2.5 Gy per fraction) and will go to a lower total dose of 42–50 Gy. For patients in whom we are trying to relieve pain or reduce clinical signs secondary to their tumor (palliative care) and for whom we are not anticipating survival beyond 6 months, higher dose per fraction protocols of 6–9 Gy in each treatment to a total dose of 24–36 Gy are used. For definitive therapy, the standard of care is daily treatments given Monday through Friday and for palliative therapy, treatments are most often given once weekly or for some protocols two concurrent days.

THE BASICS OF TREATMENT PLANNING

Hand Planning

If we are treating an area surrounding a scar from an incompletely excised soft tissue sarcoma or mast cell tumor for example we will often use a hand plan. If no gross disease is present and it is in an area where we are not as concerned about dose to the normal tissue then we will often plan by hand. This is done by placing an appropriate margin around the scar and then calculating an appropriate dose to the desired depth, taking into account the skin and exit doses.

Computer Planning

With the advent of computer, planning radiation plans with multiple beams can be easily made using advanced imaging such as CT and MRI. Most treatment planning systems use CT scans for treatment planning since it provides density information for dose calculation and because it provides better geometric accuracy than MRI. Many of these programs will allow fusing of an MRI image to a CT scan, allowing us to take advantage of the superior soft tissue detail seen with MRI while still providing the information from the CT. This is particularly useful when planning brain tumors, which are much better visualized on MRI than CT. For most other tumor types, usually a CT alone is sufficient.

For treatment planning the patient is scanned in the position that they will be treated in using any patient positioning devices that you plan to use. This allows for the most accurate set-up later. The CT is then imported into the program. The area to be irradiated is then identified and marked. The gross tumor volume (GTV) is the visible tumor. The clinical target volume (CTV) is the GTV plus an appropriate margin for the tumor type. The margin for the CTV is based on the tumor type and its biological behavior. The planning target volume is the CTV plus an appropriate margin that takes into account patient/organ movement, set-up variation and machine limitations. While the GTV and CTV are set by the tumor itself, limitations in technology help determine the PTV. Advanced imaging, more modern equipment and patient positioning devices can all allow us to shrink the PTV.

Three-dimensional (3-D) treatment planning systems let you visualize dose on a 3-D image and also allow creation of dose volume histograms, which are graphs that let you see what volume of tissue is receiving what dose of radiation. This is useful in ensuring that the tumor is receiving the desired dose and that normal structures (such as lung, spinal cord or eyes) are getting the minimal dose possible. Individual plans can then be compared.

TUMOR RESPONSE

The effectiveness of radiation therapy depends on many factors including the type of tumor, its location, whether it is localized or not and the quality of the radiation plan as well as the ability of a facility to carry out that plan in a reproducible manner. The rest of this session will cover some of the more common tumor types treated with external beam RT and the expected outcome with treatment.

Squamous Cell Carcinoma

When treating squamous cell carcinoma location and species differences are key. While squamous cell carcinoma of the oral cavity in dogs is very responsive to treatment with a reported 1-year survival of over 75%, it is a relatively ineffective treatment for cats with oral squamous cell carcinoma. In contrast, squamous cell carcinoma on a cat's nasal planum is very responsive to radiation therapy and may be curative, while those on a dog's nasal planum are not.

Mast Cell Tumors

Most mast cell tumors can be effectively managed by surgery alone. If microscopic disease is left behind, RT can be used to treat the area. The reported outcomes are very good with 5-year survival rates of 86% reported for incompletely resected Mast cell tumors treated with radiation therapy. Grade and stage are very important in determining prognosis, but even higher-grade tumors or those that have spread to the local lymph node can be effectively treated with RT as part of their treatment protocol. In one report in dogs with grade II mast cell tumors that had metastasized to the local lymph node the median disease-free survival was 1,240 days. Dogs with grade 3 mast cell tumors are also reported to do well after surgical resection and irradiation of the primary tumor area and local lymph node with a median survival of 28 months. It would be advisable to consider chemotherapy in these patients as well to try to treat potential metastatic disease.

Soft Tissue Sarcomas

Incompletely resected soft tissue sarcomas are commonly seen. While additional surgery may be possible and curative, radiation therapy is used when surgery will not result in a complete resection or will require limb amputation. With the advent of electron therapy it is also possible to treat tumors on the thorax or abdomen without causing damage to the underlying normal tissue. While outcome depends on grade, median disease free intervals of nearly 3 years and median survival of 5 years have been reported.

Pituitary Tumors

Dogs with pituitary macroadenomas, whether or not they have pituitary dependent hyperadrenocorticism, often respond well to radiation therapy. While radiation won't necessarily control signs of Cushing's disease, it is often able to control neurological signs, improve quality of life, and extend survival compared to untreated dogs. In a recent study looking at 19 dogs treated with full course radiation therapy median survival was not reached and mean survival was 1405 days with 1-, 2-, and 3-year survivals of 93%, 87%, and 55%, respectively. Both the height of the tumor compared with the skull height and the area of the tumor compared with the brain area were prognostic for survival.

Nasal Tumors

For a more detailed description of nasal tumors please see the previous article on nasal tumors in these proceedings. In dogs, the most common tumor types include nasal carcinomas while sarcomas are less common. In cats, the most common type of nasal tumor is lymphoma. Radiation therapy is very useful in the management of nasal tumors. In a recent study of cats with nasal lymphoma treated with radiation therapy and six-months of chemotherapy median survival was 955 days. The only prognostic variable identified was cribriform plate destruction. For dogs, median survivals for carcinomas range from 8 to 12 months and for sarcomas median survival ranges from 12 to 18 months.

Brain Tumors

The most commonly treated brain tumor in dogs is a meningioma. There are several studies, which suggest that radiation therapy used alone or in conjunction with surgery can extend life. In one study dogs treated with surgery alone had a median survival of 7 moths while those treated with RT and surgery had a median survival of 16.5 months. In another paper looking at dogs with brain masses causing neurologic signs median survival was reported at 699 days with RT.

Thyroid Tumors

Thyroid tumors are also considered to be responsive to radiation therapy. Surgery and radiation are often combined in the treatment of these tumors with reported median survivals of over 2 years. Even with large non-resectable tumors, outcome can be good. One study reported a median survival of over 24 months while another reported progression-free survival rates of 80% at 1 year and 72% at 3 years.

Oral Melanoma

Radiation therapy can be used to treat local disease in dogs and cats with oral melanoma. Most often this is done using a coarsely fractionated protocol with reported median survival rates of 6 to 8 months. Most dogs do not die from their local tumor but of metastatic disease. In cats with oral melanoma treated with radiation therapy there is a case series, which reported a median survival of 146 days.

Osteosarcoma

Radiation can be used to help palliate the pain caused by primary bone tumors such as osteosarcoma in dogs. It can be very helpful in cases where owners do not want to amputate the affected limb but do want to try to control the dog's pain and extend life. Median survival has been reported at 4 to 6 months with about 75% of the dogs having some relief of their pain.

Injection Site Sarcomas

Radiation therapy plays an important component in the treatment of injection site sarcomas in cats. Either in the preoperative or postoperative setting radiation extends both the progression free interval and overall survival. Median survival has been reported as high as two years.

References are available from the author upon request.

DEALING WITH COMPLICATIONS FROM CHEMOTHERAPY

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Chemotherapy agents carry the risk of complication. Complications can be broken down into those associated with administration such as anaphylaxis and extravasation reactions and those associated with toxicity of the drug itself. The most common toxicities associated with chemotherapy drugs relate to their effects on rapidly dividing cells, leading to bone marrow suppression (myelosupression and thrombocytopenia) and gastrointestinal side effects (vomiting and diarrhea). There are, however, other toxicities found with some commonly used drugs including cardiac, renal, liver, and bladder toxicities.

ALLERGIC/ANAPHYLACTIC REACTIONS

Certain chemotherapy agents are known to produce allergic or anaphylactic reactions in some or even a majority of patients. L-asparaginase and doxorubicin are the two commonly used agents that can result in these reactions. Other drugs that are used less frequently such as paclitaxcel (Taxol) are known to cause severe allergic-type reactions.

Doxorubicin reactions often are seen during administration and are secondary to the degranulation of mast cells. Dogs will often shake their heads and on occasion salivate when having a reaction. The infusion should be stopped. Administration of dexamethasone (0.2 mg/kg IV) and diphenhydramine (2 mg/kg IM) can be helpful. Blood pressure should also be monitored. If the reaction was not severe, the infusion can be restarted but should be given at a slower rate. The next time a patient is to receive the drug they should be premedicated with dexamethasone and diphenhydramine before the drug is given and monitored closely.

L-asparaginase has also been associated with anaphylactic reactions either soon after or as late as several hours after administration. As L-asparaginase is a protein, which the immune system can react to anaphylaxis is more likely to happen when the drug is used multiple times. Owners should be advised of the possibility of a reaction if the patient is released soon after administration. Patients should be treated symptomatically based on the severity of signs. If the drug is to be given multiple times, then premedication with dexamethasone and diphenhydramine is advised.

BONE MARROW SUPRESSION

As most chemotherapy agents hit rapidly dividing cells, we see bone marrow toxicity commonly in our patients; however for the most part they remain non-symptomatic. The toxicities seen relate to the circulating half-life of the cells the marrow produces. While neutrophils stay in circulation only for hours, platelets can stay in circulation for about a week and red blood cells stay in circulation for 3 to 4 months. This explains why we see neutropenia most commonly followed by thrombocytopenia and anemia is rare.

The nadir refers to the time point when the agent has the most effect on circulating cell counts. For most chemotherapeutic agents the nadir for neutrophils is about 7 to 10 days. This is why it is recommended to repeat a CBC at that time. There are some exceptions to this rule. For example, carboplatin in dogs has a nadir of 10 to 14 days, cisplatin has a double nadir of about 7 and 17 days, and CCNU is less predictable and can nadir at 7 days but also later over the 3-week period. For drugs like chlorambucil and melphalan, which are administered several times a week to daily, CBCs should be checked monthly.

A CBC must be checked before giving any myelosupressive drugs. If the absolute neutrophil count is less than 2,000 cell/μL and the nadir CBC revealed a neutrophil count less than 1,500 cells/μL then it is advisable to consider reducing the dose on the next administration by 10% to 20%. While dose reductions may be necessary it is important to remember that you are also decreasing the intensity of the cancer therapy and are also sparing the tumor.

If the neutrophil count is less than 2,000 to 2,500 cells/μL then the dosing should be delayed until the neutrophil count recovers; generally this will happen within 5 to 7 days. If the patient has a nadir neutrophil count of less than 1,500 cells/μL, is not ill, and does not have a fever then prophylactic oral antibiotics should be started for a 5- to 7-day course. Clavamox and enrofloxacin at standard dosing are good choices. Some clinicians also like to use trimethoprim-sulfamethoxazole (TMS). If the patient appears ill, even if they do not have a fever (without neutrophills the body may not be able to mount a fever), the patient should be treated aggressively with IV fluids, IV antibiotics (eg, ticarcillin/clavulanate 50 mg/kg IV TID), blood and urine cultures, and supportive care. Often these patients will recover rapidly with this high level of care. Subsequent chemotherapy treatments should also be dose reduced by at least 20% and the patient should be monitored closely. The owner can monitor body temperature at home and the CBC values should be closely watched.

Platelets counts can also be affected and chemotherapy should be delayed and dose reductions considered if the platelet count falls below 75,000. It is particularly important to watch platelet counts carefully when using CCNU. Permanent progressive thrombocytopenia is possible. If platelet counts decrease between treatments, even if they are still in the normal range, a dose reduction or increased time between administrations is necessary. If the platelet counts do not recover then the drug should be discontinued.

GASTROINTESTINAL COMPLICATIONS OF CHEMOTHERAPY

One of the major complications of chemotherapy and probably the thing that causes the most owner concern is gastrointestinal toxicity, which includes nausea, anorexia, vomiting, and diarrhea. Different agents have different probabilities of causing differing degrees gastrointestinal signs. Some of the agents used with a high likelihood of causing GI signs are cisplatin, dacarbazine, mustargen, and streptozotocin. Agents with a moderate chance of causing GI signs include carboplatin, cyclophosphamide, cytosine arabinoside, doxorubicin, methotrexate, and 5-fluorouracil. The time to onset of signs also varies ranging from during the infusion until 3 to 5 days after treatment. In either case if vomiting is not well controlled it is important that the patient be provided with good supportive care early on. Clinical signs can become very severe and the patient can decompensate either leading to longer hospital stays or death or euthanasia if treatment is not started promptly. Besides starting antiemetics, IV fluids are essential if the patient cannot drink water without vomiting. In less severe cases subcutaneous (SQ) fluids and oral antiemetics as outlined below may be sufficient.

As many of our oncology patients are older, they may be on additional medications for concurrent disease that may predispose them to increased side effects. The use of NSAIDs and corticosteroids can exacerbate chemotherapy related gastrointestinal toxicity. Of course these other drugs may be necessary for the patient's quality of life, but it may be possible to limit there use right at the time chemotherapy is given.

It is important to rule out other causes of gastrointestinal signs, such as obstruction, progression of the patient's tumor, renal failure, diet change, pancreatitis and infectious causes. Physical examination, CBC, chemistry panel, abdominal ultrasound, radiographs, fecal examination and history can be helpful in ruling out these causes.

ACUTE CHEMOTHERAPY-RELATED NAUSEA AND VOMITING

Acute vomiting is most associated with drugs of high emotogenic potential and occurs within 24 hours of drug administration. Cisplatin is the drug most commonly associated with acute vomiting. Cisplatin-induced vomiting can often be avoided by pretreatment with butorphanol used in addition to maropitant or ondansetron. Doxorubicin is more often associated with anorexia in the acute phase of treatment. This is likely related to nausea. Concurrent or even pretreatment with oral metoclopramide or maropitant can be effective in treating patients who become anorexic after treatment. In reviewing the toxicity of doxorubicin in a protocol for the treatment of osteosarcoma we found that there were 2 reported episodes of inappetance and 4 patients experienced vomiting out of the 82 doses given. Most of the occurences were self-limiting and required only symptomatic treatment. No dogs were hospitalized.

DELAYED CHEMOTHERAPY-RELATED NAUSEA, VOMITING, AND DIARRHEA

Although the incidence rate is low many chemotherapeutic agents can cause delayed vomiting. Most often clinical signs start between 2 and 5 days after drug administration. Many chemotherapeutic drugs have cytotoxic effects directly on mucosal and crypt cells of the small intestine. Chemotherapeutic drugs that are commonly used in veterinary patients that can lead to an ulcerative enteritis include actinomycin D, cytosine arabinoside, doxorubicin, DTIC, methotrexate, and vincristine. The clinical features include pain, bleeding, vomiting, ileus, and diarrhea. Many cases can be treated on an outpatient basis with oral antiemetics but with severe cases supportive care with IV fluids, antiemetics, potassium supplementation, and pain medication started soon after the start of clinical signs often results in a positive result. With therapy clinical signs usually resolve in 2 to 4 days as the mucosa and crypt cells are replaced.

Chemotherapy induces diarrhea by disrupting the normal processes that regulate fluid absorption and secretion, by altering GI defense mechanisms, and by damaging the mucosa of the small and large intestine. Diarrhea associated with chemotherapy is often self-limiting, but on occasion can be severe. Supportive care is the cornerstone of therapy. Ensure that the patient has adequate fluid intake so as not to become dehydrated. If melena is seen GI protectants (H2 blockers and sucralfate) are indicated. In cases where colitis is suspected metronidazole at 30 mg/kg PO divided BID or Sulfasalazine (10–25 mg/kg PO TID-QID) can be very effective.

Vincristine use has been associated with paralytic ileus. This is thought to be part of the toxicity, which is also manifested as a peripheral neuropathy that is sometimes seen with use of this drug. Paralytic ileus can be associated with the first use of the drug or after it has been used multiple times in a patient. Once a patient has shown gastrointestinal signs after the use of vincristine, care should be taken with using this drug again as the clinical signs tend to progress with subsequent dosing. The onset of clinical signs can be from several days after administration to as long as two to three weeks after the drug was given.

Diagnosis is made based on clinical signs, abdominal radiographs, which reveal dilated gas filled bowel loops and ultrasound, where a lack of peristalsis can be identified. Ultrasound of these patients may be difficult if there is a large amount of gas in the intestines. It is important to rule out intestinal obstruction, as the signs are similar and treatment markedly different.

Treatment is based on supportive care and depending on severity, can take several weeks for resolution of signs. Hydration should be maintained with the use of IV fluids. After an obstruction is ruled out a metoclopramide CRI (1.1–2.2 mg/kg/24 hr) can be helpful. As paralytic ileus can be painful analgesics should used. If the patient has constipation and no vomiting then a laxative such as laxatone can be administered. If there is fecal impaction then enemas may be helpful. If the patient is not able to eat for more than several days then nutritional support is essential. In a review of lymphoma cases treated at UC Davis with a multi-drug protocol 3 dogs out of a total of 39, developed paralytic ileus during the course of their treatment.

Table 1. Antiemetics

Drug	Dose	Mechanism of Action
Metoclopramide	Oral, IV, SQ, IM: 0.2–0.4 mg/kg CRI: 1 mg/kg/24hrs	Dopamine antagonist at the CRTZ. At higher doses may be a 5-HT_3 receptor antagonist. Also increases lower esophageal sphincter tone and increases GI motility
Ondansetron (Zofran)	Oral: 0.5–1 mg/kg BID to TID IV: 0.1–0.5 mg/kg IV over 15 minutes TID or 30 minutes before cisplatin infusion	Serotonin Antagonists (5-HT_3 receptor antagonists) Peripherally: Serotonin is released from enterochromaffin cells in GI tract. Centrally blocks chemoreceptor trigger zone
Dolasetron (Anzamet)	Oral, IV: 0.5–1.0 mg/kg PO There are anecdotal reports of using the IV formulation orally to decrease costs	Serotonin Antagonists (5-HT_3 receptor antagonists) Peripherally: Serotonin is released from enterochromaffin cells in GI tract. Centrally blocks chemoreceptor trigger zone
Maropitant (Cerenia)	IV: 1–2 mg/kg IV PO: 2 mg/kg	NK-1 inhibitor acts by competitively inhibiting substance P binding in emetic center
Butorphanol	For cisplatin premedication: 0.4 mg/kg IM ½ hour before infusion SQ, IM: 0.2 mg/kg TID-QID	Opioid/narcotic. Mechanism of action is unknown, but there are opioid receptors in the chemoreceptor trigger zone and it may work through use of these receptors.

MISCELLANEOUS TOXICITIES

Doxorubicin is known to have cardiotoxicity. While it can happen at lower doses, with cumulative doses of >180 to 240 mg/m^2 many dogs will develop dilated cardiomyopathy. An echocardiogram can be done prior to starting therapy with doxorubicin to evaluate for pre-existing heart disease. A tachyarrhythmia is one of the early signs. To help protect the heart from this toxicity if using the drug at a high cumulative dose or if using this drug in dogs with preexisting heart disease, dexrazoxane (10 times the doxorubicin mg/m^2 dose) can be given 15 minutes before the infusion. The problem is that this drug is quite expensive.

Cyclophosphamide has been associated with sterile hemorrhagic cystitis. This is caused by the accumulation of the metabolites of cyclophosphamide in the bladder. Frequent walks after administration are advised to avoid the animal holding its urine. Many oncologists also prescribe furosemide (2-4 mg/kg PO BID for 3 doses) to help avoid this problem. If a patient does develop hemmorhagic cycstitis it can be very difficult to treat. Clinical signs include stanguria, polakiuria and hematuria. We generally culture the urine to look for secondary infections. Prescribing a short course of prednisone (0.5 mg/kg PO once daily) or NSAIDs may help with inflammation and discomfort. This can take weeks to months to resolve. In severe cases the bladder can be infused with DMSO, but this can be very uncomfortable so the patient will need to be sedated or anesthetized. It is important to note that once a patient shows signs hemorrhagic cystitis not to give the drug again as signs will progress.

Cisplatin is associated with nephrotoxicity. To help avoid this saline diuresis is necessary. The recommended saline infusion rates are 18.3 mL/kg/hr for 4hrs before, during and for 2 hours after the cisplatin administration. Creatinine levels should also be monitored and the drug not used if they are elevated.

CCNU has been associated with liver toxicity and liver values should be monitored for increases in ALKP and ALT. Remember that we will see some increase in ALKP if the patient is also on prednisone as part of their protocol. If the liver values continue to increase you may have to discontinue the drug.

References are available from the author upon request.

PRIMARY LUNG TUMORS

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Primary lung tumors in dogs are relatively uncommon tumors. Risk factors are yet to be identified. The most common types of primary lung tumors are carcinomas and adenocaricnomas. These can be further broken down into being of bronchial, bronchoalveolar, or alveolar origin. Squamous cell carcinoma is also seen on occasion. Uncommonly benign tumors such as adenomas are found.

Generally, older dogs are affected by this disease, with a reported median age of 10.5 years. The majority of dogs present asymptomatically. These tumors are most commonly found when taking thoracic radiographs for some other reason. If dogs are showing clinical signs, they often relate to the respiratory tract and include exercise intolerance and cough. Rarely dogs present with lameness secondary to hypertrophic osteopathy as a paraneoplastic syndrome, which can resolve with removal of the lung mass.

The majority of cases will present with a single nodule seen on thoracic radiographs, although some dogs may present with multiple nodules, indicating spread of the tumor. Differentials include a primary lung tumor, a granuloma, or a metastatic lesion. A thorough work-up including physical examination, blood work and abdominal ultrasound are indicated to look for cancer elsewhere in the body to rule out the mass being metastatic disease from another tumor. Depending on the location ultrasound, guided aspirates of a pulmonary mass may be possible, which can further help differentiate primary lung tumors from other causes. This procedure is not without risk however and results from cytology may not be diagnostic.

A CT scan of the thorax can help further rule out the spread of tumor within the lungs themselves or to the perihilar lymph nodes. CT has been shown to be more sensitive and accurate than radiographs in identifying affected lymph nodes. Several studies suggest that these tumors are highly metastastic to other areas of the lung or to the hilar lymph nodes, further supporting the use a CT scan prior to deciding on a treatment course.

Treatment of primary lung tumors most often involves surgical removal of the affected lung lobe. If possible, the hilar lymph nodes should be biopsied to look for metastasis. Most dogs recover quite well from the procedure, although may require substantial aftercare in the immediate post-operative period. There is a recent report of thorascopic lung lobectomy for the treatment of lung tumors in dogs. While this procedure is less invasive than thoracotomy, the surgeon has to be prepared to convert to a thoracotomy should it be needed, as was the case for 4 out of 9 patients in this study. In several studies, median survival for dogs with primary lung tumors treated with surgery is about one year.

There is little information regarding the use of chemotherapy for primary lung tumors in dogs. One relatively recent study suggests some efficacy for vinorelbine (15–18 mg/m^2 IV), but this has not been fully investigated.

Prognostic factors for primary lung tumors in dogs include the size of the lesion, visual identification of enlarged lymph nodes during surgery, histological type, tumor stage, the presence of clinical signs at presentation, positive surgical lymph nodes and grade. In one study, dogs who did not have visually enlarged hilar lymph nodes had a median remission duration of 365 days, while those who did had a median remission duration of 60 days. This again stresses the importance of staging the patient before treatment.

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WHAT'S NEW IN SMALL ANIMAL ONCOLOGY?

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It has been exciting to be a veterinary clinical oncologist the last ten years both in and out of the university. As the ranks of specialists and size of university faculty have expanded the last decade the profession has developed a critical mass and as result the knowledge and experience in the management of cancer in pets has markedly improved. New developments from our knowledge as to the cause of certain types of cancer, new molecular diagnostics, high tech imaging equipment to better stage disease such as computed tomography (CT) and magnetic resonance imaging (MRI), to gene therapy to treat cancer have all contributed to a very exciting time to be a clinical oncologist.

Few would disagree that the best way to treat cancer is to prevent it. Our knowledge of the association between the use of certain vaccines and other injectables and cancer in cats has expanded since the first published association between the use of rabies and leukemia vaccines and sarcoma development was published more than a decade ago. These tumors have been now linked to variety of injectables such as leufeneron, long-lasting penicillin, and rabies, leukemia, and certain panluekopenia vaccines. The common thread is an associated injection site inflammatory process caused by components within these injectables that are believed to act as promoters in the pathogenesis of this tumor. Industry has responded and provided vector-based vaccines free of adjuvants that virtually eliminate injection site inflammation, which should reduce the risk of vaccine-associated tumors in cats. These revelations have resulted in changed in changes in rabies vaccination policy in many state that have reduce the frequency of rabies vaccine administration and are likely to reduce the incidence of sarcoma in cats. Similarly changes in vaccines guildelines have reduce the frequency and number of other vaccines given to cats.

Advances in tumor diagnostics have brought the profession new diagnostics that now allow earlier diagnosis of lymphoma and transitional cell cancer (TCC) of the bladder. Bladder neoplasms are the most common urinary tract tumors in the dog. Most lower urinary tract tumors are malignant and are transitional cell carcinoma. Lower urinary tract tumors are difficult to diagnose on the basis of results of cytologic examination of the urine sediment, with only 30% to 40% cases having neoplastic cells being observed cytologically. In humans, the bladder tumor antigen (BTA) test has been used in diagnosis of bladder cancer in humans. The use of the veterinary version of this diagnostic test has been recently revaluated for detection of lower urinary tract malignancies in dogs. The V-BTA test is a latex agglutination assay for the qualitative detection of bladder tumor analytes in the urine. A recent study evaluated 229 client-owned dogs with 1) TTC of the lower urinary tract, 2) healthy control dogs, 3) unhealthy control dogs with non-TTC urinary tract disease, and 4) unhealthy control dogs without urinary tract disease. Test sensitivities were 88%, 87%, and 85% for all dogs with suspected and confirmed TCC of the urinary bladder, respectively. Test specificities were 84%, 41%, and 86% for healthy control dogs, unhealthy control dogs with non-TCC urinary tract disease, respectively. These results are better than cytology and indicate the test is a good screening test for TTC of the urinary tract in the dog.

Molecular diagnostics that are based on cancers clonality characteristics have been made available to the practitioner. This polymerase chain reaction (PCR)-based technology allows for amplification of antigen binding sites and B and T cells from simple a blood sample or fine needle aspirate that contain DNA. By amplifying the gene products from the sample one can analyze for similarity of the gene products. Gene products that are similar represent clonality as characteristic of cancer while normal tissues produce a diverse population of gene products. The simple tests help diagnosis lymphoma in the dog earlier and helps interrupt equivocal histopathology or cytology finding in canine patients.

New diagnostics using protonomic technology has been developed at the University of Minnesota for looking at the predisposition to injection site sarcomas. Although this technology has now been licensed to a commercial interest it is not yet available to the practitioner.

Better staging of cancer in pet is now available through the wider availability of CT to veterinary practitioners. Recent studies have identified the values of this imaging technology in patients. A recent study of 18 vaccine associated sarcoma found clinical evaluation using calibers for establishing volume underestimated the tumor volume by one half when compared to tumor volumes were established from the CT examination.

Another study compared the use of tradition radiographs and CT in evaluating the thoracic cavity for evidence of spread of the cancer to the lung tissue. The study was carried out in 18 dogs with know pulmonary spread of their cancer. Traditional radiographs detected only 9% of the CT detected pulmonary nodules. The threshold size for the CT in the study was approximately 1 mm while traditional thoracic radiography was 7 to 9 mm. The marked increased sensitivity of thoracic CT or traditional radiography is rapidly making CT the standard of care for detecting pulmonary spread of disease.

Another study establishes the value of fine needle aspiration cytology in evaluation for evidence of regional lymph node spread of neoplasia. When the sensitivity and specificity of physical examination, fine needle aspiration cytology where compared to histopathology of regional lymph nodes in dogs and cats with cancer the sensitivity and specificity of physical examination was only 60% and 72%, respectively, while the sensitivity and specificity of fine needle aspiration cytology were 100% and 96%, respectively. The good correlation between fine needle aspiration cytology and histological examination of the entire lymph node suggest this technique is reliable and less expensive means of staging veterinary patients with cancer.

The use of serum alkaline phosphatase levels as a prognostic indicator in canine osteosarcoma has been evaluated by three groups. Serum alkaline phosphatase (ALP) levels have been found in one study to be of prognostic significance in a series of 75 dogs with appendicular osteosarcoma. Archived sera were analyzed for total ALP (tALP) and bone ALP (bALP) activities. Dogs with increased (outside normal range) preoperative tALP had a significantly decreased disease-free interval (DFI) (170 days vs. 366 days) and survival time (177 days vs. 495 days) while dogs with increased preoperative bALP had a significantly decreased DFI (147 days vs. 430 days) and survival time (218 days vs. 546 days). In addition, postoperative (40 days) increased bALP was significantly associated with shorter DFI and survival.

On the treatment front new knowledge from a study that looked at the value of l-asparginase in the management of lymphoma in dogs is likely to change the way we use this drug in the treatment of this disease. The recent study looked a the value of l-asparginase in the CHOP-based combination protocol for canine lymphoma and found little contribution of the l-asparginase to remission rate or duration and suggest exclusion of l-asparginase in combination protocols. The real value of this drug may be in most appreciated when it is reserved for use in rescue treatment protocols or in patients that have failed to obtain a remission after an induction protocols.

The value of radiation therapy in the treatment of mast cell disease was evaluated. 56 dogs were treated with megavoltage radiation for mast cell neoplasia. Total radiation dose ranged from 45 to 57 Gray (Gy), dose per fraction ranged from 3.0 to 4.0 Gy, and radiation treatment time ranged from 14 to 28 days. Median disease free interval (95% CI) was 32.7 (19 to 70) months. Median disease-free interval for dogs older than 7.5 years was 15 (lower limit 7) months as compared with 62 (lower limit 20) for dogs younger than 7.5 years of age ($P = 0.006$). Median disease free interval for dogs with measurable disease was 12 (lower limit 5) months as compared with 54 (32–70) months for dogs with microscopic disease ($P = 0.006$). Radiation treatment time was also significantly related to disease-free interval. Median disease-free interval for dogs treated longer than 22 days was 12 (7–19) months as compared with greater than 50 (lower limit 20) months for dogs treated in 22 or fewer days ($P < 0.001$). More recurrences were observed in dogs treated with 3-per-week fractionation and suggests that tumor proliferation in the interfraction interval may be important. Sex, tumor location, histologic grade, WHO clinical stage, number of radiation fractions, total radiation dose, and dose-per-fraction, as well as the following "yes/no" variables: steroids given, surgery prior to radiation, lymph nodes irradiated, and development of another mast cell tumor did not appear to influence median disease free interval or survival. Data presented herein support megavoltage radiation as an effective treatment for canine mast cell neoplasia, and suggest that disease-free interval in dogs treated with daily fractions may be longer than that achieved with alternating day fractions.

Complications of chemotherapy treatment are not more epitomized than the extravasation of doxorubicin. The incidence of extravasations of chemotherapeutic agents in human is reported to range from 0.1% to 6% the rate of extravasation in veterinary medicine is unknown. A recent report of the successful use of dexrazone after the extavasation of doxorubicin suggests that this complication of chemotherapy maybe better managed in the future. Dexrasone was administered IV at ten times the dose of doxorubicin given to the patient with not apparent side effects and prevented the severe necrosis often observed after the extravasation of doxorubicin.

The new advances in the treatment of cancer have moved forward into the new era with the recent approval of the first canine melanoma vaccine for the treatment of oral malignant melanoma. Canine patients with advanced disease (WHO stage II, III or IV) have a reported median survival time of 1 to 5 months with standardized therapies. A combination of hypo-fractionated radiation therapy and chemotherapy have a reported median survival time of one year in stage I oral CMM. Unfortunately, response rates to chemotherapy in humans or dogs with advanced melanoma range from 8% to 28% with little evidence that treatment improves survival Active immunotherapy in the form of vaccines represents one potential therapeutic strategy for melanoma. The advent of DNA vaccination circumvents some of the previously encountered hurdles in vaccine development. One way to induce immunity against a tissue specific differentiation antigen on cancer cells is to vaccinate with xenogeneic antigen or DNA that is homologous to the cancer antigen. It has been shown that vaccination of mice with DNA encoding cancer differentiation antigens is ineffective when self-DNA is used, but tumor immunity can be induced by orthologous DNA from another species. Melanoma differentiation antigens of the tyrosinase family were chosen as targets for this tumor. Tyrosinase is a melanosomal glycoprotein, essential in melanin synthesis. Approximately 400 dogs with previously histologically confirmed spontaneous malignant melanoma were treated with xenogeneic DNA vaccinations. All dogs were clinically staged according to the WHO staging system of stage I (tumor < 2-cm diameter), II (tumors 2- to 4-cm diameter, negative nodes), stage III (tumor > 4 cm and/or positive nodes) or stage IV (distant metastatic disease). Dogs with WHO stage II, III or IV histologically confirmed malignant melanoma were allowed entrance onto the study due to the lack of effective available systemic treatments. The signalments of dogs on this study have been similar to those in previously reported CMM studies. Dogs with stage II-III loco-regionally controlled CMM across the xenogeneic vaccine studies have a Kaplan-Meier (KM) median survival time (MST) of > 2 years (median not yet reached). The KM MST for all stage II-IV dogs treated with huTyr, muGP75 and muTyr are 389, 153 and 224 days, respectively. The KM MST for stage II–IV dogs treated with 50 µg MuTyr, 100/400/800 µg HuGM-CSF or combination MuTyr/HuGM-CSF are 242, 148 and > 900 (median not reached, 6/9 dogs still alive) days, respectively. For dogs on the Phase Ib MuTyr/HuGM-CSF/Combination trial, significant differences in MST were noted across pre-vaccination stage (stage IV MST = 99 days, stage III = 553 days and stage II > 401 days, $P < .001$). The results from dogs vaccinated with huTyr were published in 2003 (Bergman et al, Clin Cancer Res, 2003). The results of these trials demonstrate that xenogeneic DNA vaccination in CMM is: 1) safe, 2) potentially therapeutic with results in stage II/III local-regional controlled disease and dogs receiving MuTyr/HuGM-CSF combination.

From the recognition of new cancer etiologies to better diagnostics, staging technologies and better treatments, clinical veterinary oncology has become of age.

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HOW I TREAT PARANEOPLASTIC DISSEMINATED INTRAVASCULAR COAGULATION

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PATHOPHYSIOLOGY

The term *paraneoplastic syndrome* is used to describe a large and diverse group of conditions where underlying neoplasia leads to a change in body function distant from the site of the tumor. Paraneoplastic disseminated intravascular coagulation (DIC) is a specific pathologic process caused by underlying neoplasia and characterized by uncontrolled systemic formation, followed by lysis, of fibrin clot. While many animals with paraneoplastic DIC have dramatic hemorrhage at the time of clinical presentation, it is important to recognize that the underlying pathologic defect is actually one of excessive clot formation: bleeding does not occur until reserves of platelets and clotting factors are exhausted. DIC is found in association with a wide variety of neoplastic and non-neoplastic conditions, but regardless of the underlying disease it is characterized by a four common features: a stimulus that triggers excessive clot formation; systemic formation of microvascular thrombi leading to widespread tissue damage; failure of perfusion of vital organs; and, eventual depletion of hemostatic factors. Common sequelae include damage to the central nervous system, kidneys and lungs, excessive bleeding, and death. Paraneoplastic DIC is probably seen most commonly in small animals with hemangiosarcoma, lymphoma, inflammatory mammary carcinoma, mast cell tumor and systemic histiocytic sarcoma, but it could occur in association with virtually any type of cancer.

Normal hemostasis is a carefully controlled and localized process. DIC is characterized by loss of one or more of the mechanisms that normally localize coagulation, and may be initiated by abnormalities in any of the four major components of hemostasis: blood vessels, platelets, clotting factors, or clot lysis. Loss of vascular integrity with exposure of large areas of damaged vascular endothelium may cause platelet adhesion and aggregation, resulting in uncontrolled clot formation. DIC can be initiated when platelets become abnormally "sticky," and form platelet plugs without pre-existing vascular injury. DIC may also result if coagulation factors become activated abnormally. This is most likely to occur when large quantities of intravascular tissue phospholipid are present, such as with a large, necrotic tumor. Tissue phospholipid within the systemic circulation provides a surface for clotting factor activation, and widespread activation of the coagulation cascade leads to excessive formation of fibrin clot. Clotting factors are consumed and eventually depleted: the concentrations of fibrinogen and the labile cofactors V (proaccelerin) and VIII (antihemophiliac factor A) decline first and become limiting because they are used once and destroyed. Finally, abnormalities involving the fourth and final component of hemostasis, clot lysis, may initiate or promote DIC as well. Massive fibrinolysis mediated by the serine protease plasmin produces fibrin split products (FSPs, also known as fibrin degradation products or FDPs), and the capacity of the mononuclear phagocyte system to clear FSPs may be overwhelmed if the quantities in circulation are high enough. FSPs coat platelets and prevent normal platelet aggregation, and inhibit the formation of fibrin cross-links as well. DIC can result when ineffective clot synthesis continues in an attempt to prevent hemorrhage. Reserves of functional platelets and coagulation factors are eventually depleted, and spontaneous bleeding begins or worsens. Accelerated fibrinolysis may be of clinical significance in animals with urinary tract cancer, especially when the prostate gland is involved. Urokinase, a tissue activator of plasmin present in the urinary tract, may be released in large enough quantities to cause systemic activation of plasmin, leading to widespread clot lysis, FSP production and DIC.

DIAGNOSTIC EVALUATION

Most animals with paraneoplastic DIC are critically ill by the time they are presented for evaluation. Thus, rapid but thorough clinical assessment is essential if treatment is to be successful. Initial evaluation should include a medical history, with particular attention to the presence of underlying tumor. Physical examination must then focus not only on abnormalities associated with the tumor, but also any evidence supporting the presence of a coagulopathy. The clinician must maintain a high index of suspicion: clinical signs may be subtle, and may be associated with defects in any of the four major components of hemostasis. Finally, the critical nature of DIC cases often dictates that laboratory testing be performed concurrent with the initial clinical assessment. The minimum database for an animal suspected of having DIC should include a platelet count, peripheral blood smear, prothrombin time (PT), activated partial thromboplastin time (aPTT), FSP titer, and fibrinogen concentration (if available). These diagnostics are performed in addition to testing necessary to evaluate the animal's underlying neoplastic disease. The latter commonly includes a serum biochemical profile, urinalysis, chest and abdominal radiographs, and abdominal ultrasonography, with other tests ordered as indicated depending on the individual case.

The earliest laboratory evidence of DIC is generally a decreased platelet count. The normal circulating platelet half-life is approximately 4 to 5 days, and sudden losses cannot be replaced: thus, the peripheral count closely reflects the degree of ongoing intravascular coagulation. In addition to assisting in the initial diagnosis of DIC, daily platelet counts are useful in critical animals receiving treatment for DIC, allowing assessment of the efficacy of therapy. However, when evaluating counts it is important to remember that the normal range is very wide: while a 200 x $10^3/\mu L$ count may still fall within the normal range, if the platelet count was 400 x $10^3/\mu L$

24 hours ago this may still represent a clinically significant change. Other measures of coagulation are less sensitive in detecting early DIC. The aPTT and PT are prolonged once depletion of fibrinogen and factors V and VIII is sufficient to affect fibrin clot formation. However, both of these tests are less useful for the detection of small changes in coagulation, and they are not as valuable for following the dynamics of the DIC process as the platelet count. FSP concentrations eventually rise to detectable levels as well, but not until the mononuclear phagocyte system is overwhelmed. FSP titers reflect rates of both FSP production and removal, and negative or very low titers may be misleading not only early in the course of DIC, but late in DIC as well, when there is very little fibrin substrate remains.

Two additional tests that aid in assessment of animals with possible paraneoplastic DIC are D-dimer concentration and antithrombin concentration. Plasmin is the serine protease responsible for normal fibrin clot dissolution, but it also has activity against fibrin's inactive precursor, fibrinogen. Positive FSP titers may obviously be misleading if a substantial proportion of the FSPs measured come from the action of plasmin on fibrinogen rather than fibrin, and this is where determination of D-dimer may be useful. Fibrin clots are stabilized after formation through crosslinking by factor XIII, and when a stabilized clot is lysed into FSPs some of the fragments will contain this crosslink. These fragments are known as "D-dimer," and their plasma concentration can be measured to confirm that stable fibrin clot is actually being lysed. Antithrombin is a normal physiologic inhibitor of coagulation, and ongoing consumption of antithrombin during DIC may exacerbate uncontrolled clot formation and depletion of clotting factors. Plasma antithrombin concentrations are predictive of outcome in people with DIC secondary to sepsis, a worse prognosis being associated with low plasma antithrombin levels. Serial plasma antithrombin concentrations can also be used to guide therapy for DIC.

TREATMENT OF PARANEOPLASTIC DIC

The single most important factor in the successful management of animals with paraneoplastic DIC is identification and treatment of the underlying tumor. Primary antineoplastic therapy may involve surgery, radiotherapy or chemotherapy, depending on the diagnosis. Concurrent therapy to stabilize tissue perfusion and clotting function is clearly indicated as well, especially before affected animals can undergo primary therapy in the form of surgery. However, it is absolutely essential to understand that normalization of clotting function without removal of the initiating malignancy is an unreasonable expectation. If treatment for the underlying tumor is not effective then the animal is highly unlikely to survive, regardless of the ancillary therapy that is provided.

Intravenous fluid therapy is arguably the most important supportive treatment for animals with paraneoplastic DIC. Fluids are used to expand intravascular volume and maintain tissue perfusion by inhibiting microvascular thrombus formation. Intravenous colloid and pressor therapy may also be necessary to maintain adequate end organ perfusion in some animals that are hypoproteinemic or persistently hypotensive. Next, consumed blood constituents are replaced through administration of blood products. Fresh frozen plasma (FFP) replaces both clotting factors and control proteins such as antithrombin. Approximately 6 to 12 mL FFP/kg body weight is recommended per dose, and multiple doses are virtually always required. Response to therapy can be measured most effectively by following serial platelet counts and fibrinogen concentration; FSPs may actually increase after initiation of FFP therapy, as additional substrate in the form of fibrinogen is provided. Administration of fresh whole blood may be considered if FFP is not available, but valid indications as well as potential contraindications must be carefully considered. Fresh whole blood certainly contains the clotting factors that are needed by the animal with DIC. However, whole blood is often administered with the mistaken assumption that substantial numbers of platelets will also be delivered. In fact, the quantity of platelets in whole blood is quite low and unlikely to provide clinical benefit when thrombocytopenia is severe. It is also important to recognize that whole blood is contraindicated for some animals with paraneoplastic DIC. For instance, animals with hemolysis as a contributing cause of DIC could experience worsening of their disease after administration of whole blood; in addition, hemolysis caused by overtransfusion of red cells could exacerbate DIC secondary to any underlying cause.

Heparin is a controversial treatment that may be considered for some veterinary cancer patients with DIC. Few human or veterinary publications have documented objective evidence of benefit, but controlled prospective studies are difficult to design because the causes of DIC are so variable. Heparin theoretically stops the excessive clot formation that occurs in DIC by increasing the binding and inactivation of serine proteases by antithrombin. Sufficient antithrombin is therefore required for heparin to have activity; it has no inherent anticoagulant activity on its own. Based on its mechanism of action, heparin therapy is most logical for animals with DIC caused by abnormal activation of clotting factors. Hemangiosarcoma is an example of a tumor likely to fit in this category. The recommended dose of heparin is highly variable, with most veterinary authors recommending 50 to 100 IU/kg IV, IM or SQ two to four times daily. Concurrent administration of FFP should be considered to ensure antithrombin concentrations are adequate to allow a response.

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COMMON ERRORS IN THE MANAGEMENT OF DOGS AND CATS WITH CANCER

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Neoplastic disease is common in pet dogs and cats. Improved veterinary care and nutrition, among other factors, have resulted in an increasingly geriatric pet population, and cancer is a major cause of death in these animals. There is no doubt that the management of dogs and cats with cancer can be challenging, but it is now an integral part of routine veterinary practice. Fortunately, it turns out that most cancers in dogs and cats are very treatable, even though they may ultimately be incurable. The last 20 years have seen exponential growth in the field of veterinary oncology, and the wide availability of sophisticated therapies has resulted in excellent quality of life and survival times that are no different from those seen with other chronic diseases for many affected animals. The expectations of pet owners have changed as well. They feel greater acceptance of the strong emotional attachment that they have to their pets, and they will do everything within their power to preserve this bond. Easy access to information through the internet and lay press also means these people are often very well informed, and they know about recent advances in both human and veterinary oncology and are committed to taking advantage of them for their animals. Veterinarians need to be knowledgeable about common cancers in dogs and cats and the options for treating them, and they need to be able to convey this information in an understandable and positive way to pet owners. This article outlines some of the most common errors made by veterinarians managing these cases on a day to day basis, and make recommendations on how they can be avoided.

MAKING ASSUMPTIONS ABOUT THE OWNER

Veterinarians often make two risky assumptions with respect to the owner of a dog or cat with cancer. First, they make a conclusion or value judgment about the course of action the owner will or should take in diagnosing and treating their animal. Second, they assume they know how much money the owner has and is willing to spend on their animal. Unfortunately, if the veterinarian is incorrect in either assumption this can have lasting and damaging effects on their relationship with the client. When advising the owner of a dog or cat with cancer, it is understandably difficult to separate your personal feelings about what is best, what is fair, or what you might do yourself given a similar situation, from what is best for that individual client and their animal. To a much greater degree than most diseases that veterinarians deal with, there are likely to be biases and emotions about cancer and its treatment that arise from personal beliefs and experiences. Despite this, it is absolutely essential to remember that the "best" course of action for an individual owner and their animal with cancer is highly variable, impossible to predict, and an intensely personal decision. The veterinarian's job is not to tell the client what is right, it is to present all of the options in a clear, objective and understandable way and then allow the owner to choose the one that fits best for them. Some owners will go much further than we may think is reasonable, but it is their animal and this is their prerogative. Just as frustrating are the owners that give up immediately, when their pet has treatable or even curable disease. Again, though, it is their animal and this is their privilege, not ours.

A related and equally dangerous assumption to make about an owner is how much money they are going to spend. Just because an owner is wealthy does not mean they want to– or should– spend thousands of dollars treating their pet for cancer. Alternatively, just because an owner has limited financial resources does not mean they will not find some way to pay for a very expensive, complicated course of therapy. Once again, the best course of action for the veterinarian is to simply present the options in the most objective way possible, with as accurate an estimate of the associated costs as is feasible. Assuming ahead of time what any owner will do or spend can result in a very uncomfortable and negative interaction that eventually ends with the loss of the client.

CATS ARE JUST LIKE DOGS, RIGHT?

Probably the most important thing to remember about cats with cancer is that they are not dogs. Most veterinary studies that have examined tumor biology and response to anticancer therapy have been conducted in the dog. However, direct application of this knowledge to the cat should be undertaken with great care, if at all: critical differences between the two species exist. First, the biologic behavior of common tumors differs considerably. For example, mammary tumors in the dog are histologically heterogeneous but tend to have a favorable prognosis: 3 out of 4 dogs will have extended disease-free survival after surgery alone. In contrast, mammary cancer in the cat is a very homogeneous but highly malignant disease. Almost all cats have mammary carcinomas, and even if the primary tumor is resected metastasis is highly likely and survival times are relatively short. Another important difference between the two species is that response to treatment can vary widely. For instance, dogs with lymphoma that are treated with CHOP-based chemotherapy have an 80% to 90% chance of achieving a complete clinical remission, with an expected median survival time of 12 to 14 months. Their feline counterparts that receive CHOP-based chemotherapy, on the other hand, have only a 60% likelihood of complete remission and a much shorter median survival time of 7 to 9 months. Finally, expected treatment-related toxicities can be distinctly different between cats and dogs. Doxorubicin is arguably the single most effective drug included in the CHOP protocols used to treat lymphoma. However, even though it causes a distinctive and life-threatening dilated cardiomyopathy in the dog, this complication is rare in the cat. Nephrotoxicity is a much more serious concern in this species. Veterinarians may be more comfortable with their knowledge base in canine oncology, and this is understandable based on the emphasis that has existed in the veterinary literature. However, they should always consider the possibility that what they know to be true in a dog may in fact be almost the complete opposite in a cat.

SYSTEMIC THERAPY FOR LOCAL DISEASE??

One of the most basic principles of cancer therapy is to match the treatment with the biologic behavior of the disease. Cancers can be divided into two large categories based on their biologic behavior: local and systemic. Localized cancers may aggressively invade surrounding normal tissues, but they tend to be either late to metastasize, or do not metastasize at all. Examples of typical local tumors include soft tissue sarcomas, and most mast cell tumors in the dog. These tumors are best treated with aggressive local therapy: almost always surgery, and often radiotherapy as well. On the other hand, systemic tumors either involve multiple anatomic sites at the time of presentation (canine lymphoma), or metastasize widely and aggressively during the course of the disease (canine osteosarcoma). Surgery and radiotherapy are not effective by themselves in this setting, and the only way to address all known and unknown sites of disease is with systemic therapy, or chemotherapy.

The "local therapy for local disease, systemic therapy for systemic disease" rule applies in virtually all cases. Inadequate or unsuitable treatment recommendations can be avoided by carefully researching the expected course of disease before suggesting a particular course of therapy. It is not logical to restrict treatment to aggressive and complicated local therapy in an animal that is ultimately going to die of metastasis. For instance, it would be a waste of time and money to perform a complicated limb-sparing procedure in a dog with osteosarcoma without also administering chemotherapy to treat metastatic disease. That does not mean that aggressive local therapy is unreasonable, it just means that all aspects of the biologic behavior of the tumor have to be considered when designing a comprehensive course of therapy. Conversely, it does not make sense to expose the entire animal to potential toxicity using systemic treatment when local therapy would be more effective. One of the best and most commonly encountered examples of this is the dog with a localized mast cell tumor that is given systemic corticosteroids or other chemotherapy after an incomplete surgical resection. Recent studies looking at outcome in dogs with grade II mast cell tumors indicate that over 80% of them will enjoy years of complete disease control after surgery alone: clear evidence supporting the fact that this is usually a local disease. The most appropriate course of action after incomplete surgical resection of localized mast cell tumor is more surgery or perhaps radiotherapy, not chemotherapy.

PITFALLS OF CYTOPATHOLOGY

There is no doubt that the practice of veterinary oncology would be absolutely impossible without the contribution of clinical pathologists. However, a common error made by veterinarians managing dogs and cats with cancer is to interpret the results of fine needle aspirates too literally or narrowly. There are several clear advantages of performing fine needle aspiration cytology in dogs and cats with cancer: samples can be quickly and easily obtained, using minimally invasive techniques; valuable information is generally available within a matter of hours to a couple of days at most; and, the procedure is very affordable. Despite these largely practical advantages, however, fine needle aspirates also have some disadvantages. For one thing, the sample obtained is very small and may not be representative of the entire lesion. Samples collected too far into the periphery of the lesion may consist largely of reactive host tissues; samples taken in the center of a lesion may only contain necrotic debris. In some cases the underlying neoplastic lesion is obscured by inflammation or hemorrhage. Some tumors do not exfoliate well, providing the clinical pathologist with very little material on which to base their assessment. Finally, cellular context and microscopic structure cannot be evaluated on cytology as they are with histopathology, making the diagnosis obtained less reliable. For all these reasons, clinicians should be careful not to over interpret cytopathology results. The pathologist will always do their best to provide as precise an assessment as possible, but their ability to provide useful information is limited by the quality of the material they receive. It is the veterinarian's job to know that the bottom line diagnosis printed on the cytology report is not always going to be correct, and why. Histopathology should still be the gold standard for diagnosis in most cases, especially when a very expensive course of therapy or euthanasia is being considered.

FAILURE TO ASSESS SURGICAL MARGINS

Another error sometimes made in the management of small animal cancer patients is failure to adequately assess surgical margins. When treating locally invasive cancers such as mast cell tumor with surgery, it is absolutely essential that margins be evaluated as carefully as possible. Without this information, there is no way to objectively determine whether further surgery is needed, or whether radiotherapy might be indicated. It is also impossible to provide the client with a reliable estimation prognosis. All lesions that are worth the time and effort to surgically resect should be submitted to a qualified veterinary pathologist for complete histopathologic evaluation: this should never be optional for the owner. A complete history and clinical description of the lesion must be provided, and suspect margins tagged with suture or marked with tissue ink to allow complete evaluation. When the resected lesion is too large to submit in its entirely, multiple biopsies from all areas of the surgical margins can be submitted in a separate container; these will obviously need to be tagged or marked in some way as well. Diagrams are useful to orient the pathologist, allowing them to pinpoint the site of each margin biopsy and then provide very precise information regarding which areas may still contain tumor cells. As with cytology samples, the accuracy of the information provided by the histopathologist is totally dependent on the quality of the biopsies they receive. Margins that are in fact clean may be evaluated as possibly incomplete if the tissue sample provided is too small and does not include the periphery of the lesion. Margins that are actually dirty may also be called clean if only a portion of the resected margin is included, but the resection happens to be complete in that area.

STEROIDS!

Corticosteroids are prescribed in many dogs and cats with neoplastic disease. They are indicated because they decrease inflammation, improve appetite, and often result in a temporary improvement in quality of life. They are also very effective in inducing remission in animals with lymphoma, and are an important part of most chemotherapy protocols for this tumor. However, use of corticosteroids should always be postponed until a thorough clinical evaluation has been completed and a definitive diagnosis of neoplasia has been obtained. They should never be used as a diagnostic “test” in a dog or cat that might have lymphoma or has undiagnosed hypercalcemia. Corticosteroids are profoundly lympholytic, and their premature use may make definitive diagnosis of underlying lymphoma impossible. Once the animal’s clinical signs have responded to steroids, the only options are either to recommend an expensive course of chemotherapy for an animal that may not actually have lymphoma at all, or to withhold therapy and wait for the lymphoma to come out of remission. Corticosteroids are immunosuppressive, and if the animal has an infectious condition rather than neoplasia they may cause rapid worsening of disease. For instance, dogs with blastomycosis can sometimes appear as if they may have lymphoma, because they can have peripheral lymphadenopathy and may even be hypercalcemic. Clearly, however, corticosteroids would be a poor treatment choice in a dog with this infection. Finally, multiple studies now show that dogs treated for lymphoma have significantly shortened survival if they are given as little as 5 days of corticosteroid treatment prior to the initiation of chemotherapy. This is believed to be the result of corticosteroid-induced multiple drug resistance (mdr), where tumor cells develop cross-resistance to multiple unrelated chemotherapeutic agents after exposure to only one. The use of corticosteroids should be restricted to cases that have been fully evaluated and situations where they are clearly indicated. When an owner makes the informed decision to try corticosteroid therapy without a diagnosis and despite the potential complications it can cause, this should be documented in the animal’s permanent medical record.

LET’S JUST WAIT AND SEE…

Unfortunately, clinical procrastination is probably the most common error made by clinicians managing dogs and cats with cancer. When abnormalities related to underlying neoplasia are first detected animals are frequently sent home and instructed to recheck in a few weeks, in the hope that the identified abnormality will have resolved in the interim. A course of antibiotics or analgesics is often prescribed, more to “give the owner something to do” than in the actual expectation that it will provide any benefit. It is completely understandable that veterinarians do not want to give bad news to a long term client. However, the appropriate course of action when neoplastic disease is first found in a dog or cat is to give an honest assessment of the situation and then immediately offer full evaluation, or referral for full evaluation if necessary. If the owner makes the informed choice not to pursue diagnostics and therapy that is their choice, but they should have that choice. When an animal has cancer, waiting to see what will happen can only result in one outcome: progression of disease.

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UPDATE ON INJECTION-SITE SARCOMAS IN CATS

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HISTORY AND EPIDEMIOLOGY

Injection-site sarcomas in cats were first linked with the administration of rabies vaccines in 1991. This observation coincided with a switch by the American vaccine industry from modified live rabies vaccines to more heavily adjuvanted killed products, a change that was made because of concerns about vaccine-induced disease. In addition, the frequency of feline rabies vaccination was concurrently increased in some states and counties because of implementation of annual rabies vaccination laws. Strong epidemiologic support for a cause and effect relationship between vaccination and sarcoma development was published in 1993. Cats were proven to have an increased risk of sarcoma at vaccine sites: the risk increased when multiple vaccinations were administered in the same anatomic location, and a causal relationship was demonstrated for not only rabies vaccines, but FeLV vaccines as well. Rabies and FeLV vaccines have remained the products most commonly implicated in the pathogenesis of injection-site sarcomas, but well documented reports also exist describing tumor development associated with other vaccines as well as non-vaccine pharmaceuticals and even foreign material such as nonabsorbable suture.

The estimated incidence of injection-site sarcomas associated specifically with vaccination varies significantly from source to source, but is likely 1 to 10 in 10,000 vaccines administered. Based on the estimated size of the vaccinated pet cat population in the United States, this translates into an annual incidence of between 2,200 and 22,000 cases. Tumor development is usually seen within 3 to 12 months of injection, but may be delayed for as long as 3 years.

PATHOGENESIS

Injection-site sarcomas appear to be the result of an aberrant chronic local inflammatory response. Lesions are characterized histologically by a pronounced inflammatory component with mononuclear cell proliferation, granulation and fibrosis. These areas of inflammation blend imperceptibly into regions of atypical fibroplasia, as well as areas of mesenchymal tissue that have overt histologic features of malignancy. This lends indirect support to the prevailing theory that over time, a complex interaction between the injected medication (which may include vaccine adjuvant or antigens), the inflammatory cells within the lesion, and the individual cat's genome results in tumor development. Ultimately, tumor arises from fibroblasts, mesenchymal stem cells or myofibroblasts present at the site of inflammation. Because not all cats receiving injections develop injection-site sarcomas, inherent genetic instability or the presence of specific intracellular oncogenes is believed to be ultimately responsible for malignant transformation in affected animals. Tumorigenesis could occur in direct response to the presence of the injected foreign material, or might be the result of cytokines and growth factors that are produced as part of the inflammatory response and released into the cellular environment, where they interact with the various mesenchymal elements that eventually undergo malignant transformation. Several studies now suggest that abnormalities in the function of p53, as well as platelet-derived growth factor (PDGF) and its receptor, may play roles in the pathogenesis of injection-site sarcomas. Neither the feline leukemia (FeLV) nor the feline immunodeficiency virus (FIV) appears to be directly involved.

BIOLOGIC BEHAVIOR AND HISTOLOGY

Feline injection-site sarcomas are typically found in middle-aged to older cats, although cats of any age may be affected depending on their medical history. A specific breed or sex predilection is not reported. Lesions are usually found in anatomic locations where injections are administered: the interscapular space, the paralumbar region, and the subcutaneous tissues and large muscles of the thighs. Just like spontaneous soft tissue sarcomas, injection-site sarcomas are firm, subcutaneous masses that adhere to underlying structures. While the outward appearance and texture of these tumors may suggest a well-demarcated lesion, the actual interface between tumor and normal host tissue is usually poorly defined. Injection-site sarcomas seem more likely to exhibit aggressive local biologic behavior that their spontaneous counterparts: rapid growth and extensive local invasion through and along fascial planes is common. Some authors also believe that metastasis is more prevalent with these tumors, and cats that have extended survival are more likely to develop metastases with time.

Injection-site sarcomas are most often classified histologically as fibrosarcomas, although many other soft tissue sarcomas have been reported including myxosarcomas, leiomysarcomas, rhabdomyosarcomas, and osteosarcomas. Regardless of the specific histopathologic diagnosis, certain histologic features are usually observed. The malignant mesenchymal elements of the lesion have marked nuclear and cellular pleomorphism with a high mitotic rate and large areas of necrosis. A peripheral inflammatory infiltrate is present, containing lymphocytes, histiocytic cells and multinucleate giant cells. Adjacent macrophages containing a characteristic bluish-gray material comprised of aluminum and oxygen may be noted: aluminum hydroxide is a common component of feline vaccine adjuvants, and many pathologists consider the presence of this material to be the most definitive evidence that a feline injection-site sarcoma is specifically associated with the administration of a vaccine.

DIAGNOSTIC EVALUATION

The diagnostic evaluation of any animal with malignant disease must be sufficiently thorough to accomplish five goals: provide an accurate diagnosis; completely define the extent of disease (clinical stage); identify potential paraneoplastic syndromes; diagnose concurrent but unrelated diseases; and, establish a normal baseline for the individual patient. The minimum database for a cat with an injection-site sarcoma should include a complete blood count, serum chemistry profile, urinalysis, serologic testing for FeLV and FIV, chest radiographs (three views), and a tissue biopsy for definitive histopathologic diagnosis. Radiographs or cross-sectional imaging (CT scan or MRI) of the primary tumor is also indicated in many cats, and may play a critical role in the development of an optimal therapeutic plan. The anatomic locations in which these tumors are found can make surgical resection extremely difficult: an incisional biopsy to confirm the diagnosis followed by referral to a board certified specialist will be the best approach in some cases.

TREATMENT

Feline injection-site sarcoma is usually a locally confined malignancy that is most appropriately treated with aggressive local therapy. Metastasis may occur but is infrequent early in the course of disease; thus, patient survival depends primarily on adequate local control. Systemic therapy (ie, chemotherapy) may be administered under certain circumstances, but plays a lesser or supporting role in most cats. Two primary forms of local therapy can be considered in general for the treatment of cats with cancer, and in specific for the treatment of injection-site sarcomas: surgery, and radiotherapy.

Surgery

Surgery is the single most important component of successful therapy for feline injection-site sarcomas. It is critical to be aggressive from the outset: the first surgery probably has the best chance of cure, with some studies indicating a decreased likelihood of tumor control when multiple surgeries are performed. The definitive surgery must be planned in specific detail, using radiographs and cross-sectional imaging as necessary. Wide surgical resection is essential, and the maximal potential scope of the operation, including margins, should always be carefully considered. During the surgery itself, particular attention should be paid to several factors. All previous incisional biopsy sites should be completely excised. Surgical dissection should be undertaken through normal tissue planes only. En bloc removal of the tumor together with wide and deep 3-centimeter margins of normal tissue is recommended. When it is impossible to achieve 3-cm margins, en bloc removal to include one fascial plane beyond the anatomic compartment containing the tumor is the goal. Sarcomas should never be "shelled" or "peeled" out: residual tumor pseudocapsule will be left behind making local recurrence virtually certain. If postoperative radiotherapy is being considered, radiodense markers such as vascular clamps or stainless steel suture should be placed at the margins of the resected tumor to facilitate subsequent radiotherapy treatment planning. Finally, all resected tissues should be submitted to a qualified veterinary pathologist for examination. A complete history and clinical description of the lesion should be provided, and suspect margins tagged with suture or marked with tissue ink to allow complete evaluation.

Radiation Therapy

Complete surgical excision of injection-site sarcomas can be curative. Unfortunately, the locally invasive nature of these tumors means that incomplete resections are common. Additional local therapy is definitely indicated for cats that are confirmed to have residual local disease based on the results of histopathology. Further treatment should also be considered when the margin of resection is "clean but close," or when the surgeon feels strongly that despite a histopathologic assessment of clean margins it is still likely that tumor was left behind. A second surgery completely resecting the previous surgery site will afford adequate local control in some cats, and is a practical and cost effective alternative that should be undertaken whenever possible. However, aggressive resection of a large, contaminated surgical field may be a technical impossibility, leaving radiotherapy as the primary alternative choice to improve long-term local control. Specific radiotherapy protocols vary from institution to institution, and radiotherapists disagree about whether radiation should be delivered before or after definitive surgical resection of the tumor. Postoperative radiotherapy is used most often, and certainly has a number of advantages. These include decreased risk of postoperative complications because definitive tumor resection is not performed in a previously irradiated field; decreased likelihood that metastasis will occur during a prolonged course of radiation to the primary tumor; and, more accurate assessment of true tumor margins. Proponents of preoperative radiotherapy point to advantages such as decreased need for very large surgical resections; smaller radiation fields; and, decreased risk of tumor transplantation at the time of surgical resection because of preoperative "sterilization" of tumor margins by radiotherapy. Regardless of whether radiotherapy is applied pre- or postoperatively the inherent resistance of sarcomas to radiation means that high cumulative doses are necessary, generally between 54 and 63 Gray total dose. However, virtually all studies published to date show a significant improvement in disease free intervals and survival times when surgery and radiotherapy are combined. Median disease free intervals and survival times in cats with injection-site sarcomas treated with surgery alone are reported at 3 and 19 months respectively. When adjuvant radiotherapy is administered, reported disease free intervals have ranged between 13 and 28 months, and survival times are increased to at least 24 to 28 months with median survival times not reached in some studies.

Chemotherapy

In general, systemic chemotherapy alone is not an appropriate treatment choice for cats with injection-site sarcomas. Affected cats usually have invasive local disease, and are best treated with aggressive local rather than systemic therapy. Furthermore, sarcomas tend to be relatively chemotherapy-resistant, so a dramatic and durable response in a cat with large volume gross disease is unlikely. However, chemotherapy should still be strongly considered as a component of multimodality treatment protocols. Chemotherapy drugs such as doxorubicin and carboplatin may be used as radiation sensitizers: when given concurrently with radiotherapy they can augment DNA damage and cell kill. This in turn may improve both extent and duration of local tumor response, although acute toxicity to normal tissues within the treatment field can also be increased. At this time, improved local tumor control and duration of survival for cats with injection-site sarcomas treated aggressive trimodality therapy (surgery, radiotherapy and chemotherapy) have yet to be convincingly demonstrated, but the approach makes sense based on available data. Systemic chemotherapy is certainly indicated as well when there is proven metastatic disease, or when there is histologic evidence of increased malignancy with a high probability for future metastasis. The drug that is probably recommended most frequently in these settings is doxorubicin. Tumor progression is significantly delayed in cats that receive doxorubicin after local tumor resection, compared to cats that are treated with surgical resection alone. More recently, the alkylating agent ifosfamide has been shown to have activity against injection-site sarcomas in cats, including some animals with demonstrable metastatic disease. While these early data are encouraging, there is presently insufficient evidence to support replacing doxorubicin with ifosfamide as the first-line drug for treating cats with injection-site sarcomas. While the drug may eventually play a role in the treatment of this disease, ifosfamide is a nephrotoxin and is complicated and expensive to administer. Cats receiving it must be diuresed with saline, and require careful monitoring to avoid permanent kidney injury. Further work is needed to optimize adjuvant chemotherapy protocols for cats with injection-site sarcomas, including specific drugs, their doses and the precise scheduling of administration.

PROGNOSIS

The prognosis for feline injection-site sarcomas depends primarily on the surgeon's ability to achieve a complete resection. Thus, tumor characteristics facilitating surgical excision are associated with a more favorable outcome and the possibility of prolonged survival. The prognosis is better for small, noninvasive or superficial lesions; also, location on an extremity allowing complete resection through amputation has been associated with longer disease free intervals. If complete surgical resection is not possible, the long-term prognosis is guarded: many cats will be euthanatized because of progressive disease within a few months of the time of diagnosis.

PREVENTION

Injection-site sarcomas are probably easier to prevent than they are to treat, and many measures have been recommended to decrease the likelihood of tumor development. Meticulous and detailed record keeping is essential. Information present in the animal's medical record should include the date of all vaccinations or injections; product names, manufacturers, lot or serial numbers and expiration dates; the exact anatomic sites of administration; the name of the person administering the injection; and, documentation of informed client consent for vaccinations. Multiple vaccines should never be given in the same site, and feline leukemia virus vaccines should only be administered to those cats truly at risk. Veterinarians can consider switching to nonadjuvanted vaccines for cats, with the goal of reducing the intensity of the local postvaccination inflammatory response and thus the likelihood of inducing tumor; however, evidence directly implicating vaccine adjuvant as a primary factor in the development of sarcomas is inconsistent. If adjuvanted products are used, single dose vials are recommended so that the dose of adjuvant received by each vaccinated animal is standardized. Clients should be encouraged to monitor vaccine sites through regular palpation, and any mass detected should be treated as malignant until proven otherwise. Complete surgical resection is recommended for injection site masses that persist for longer than 2 months, are increasing in size over one month after vaccination, or are greater than 2 cm in diameter. Although fine needle aspiration cytology can be performed and may provide useful information, it is important to recognize that it is not necessarily a reliable method for differentiating inflammatory lesions from potentially neoplastic ones: because of the presumed pathogenesis of these tumors, inflammatory cells are likely to be present whether the mass is neoplastic or not. Furthermore, even if a mass is truly inflammatory and has not undergone neoplastic transformation at the time of aspiration, this does not mean that it will not do so at some point in the future. Thus, surgical resection is still the most appropriate course of action. Histologically confirmed injection-site sarcomas should be reported to the product manufacturer as well as any appropriate oversight agencies.

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HALF-BODY RADIOTHERAPY FOR THE TREATMENT OF CANINE LYMPHOMA

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Lymphoma is a commonly and successfully treated tumor in dogs. Chemotherapy is recommended in almost all cases, for two reasons. First, canine lymphoma is a systemic disease, so chemotherapy is the only way to address the animal's disease in its entirety. Second, chemotherapy is a highly effective treatment for lymphoma. CHOP-based protocols incorporating cyclophosphamide, doxorubicin, vincristine, and prednisone are the current gold standard, and complete remissions are achieved in 80% to 90% of dogs. Reported median remission durations range from 7 to 9 months, with overall median survival times in the range of 12 to 14 months.

Numerous attempts have been made to improve survival in dogs with lymphoma by making changes to the CHOP protocols in common use. Most of these have involved increasing the intensity of therapy: based on chemotherapy theory, improved responses should result if the tumor is treated more aggressively. Investigators have increased drug doses, administered drugs more frequently or even given drugs concurrently instead of sequentially. Unfortunately, the result has been unacceptable treatment-related toxicity: gastrointestinal side effects, sepsis, and more treatment-related deaths. Many owners and veterinarians are unwilling to accept such significant toxicity because quality of life, rather than quantity, is the primary concern.

New strategies are needed to improve response to therapy in dogs with lymphoma. One alternative that is currently receiving attention is multimodality therapy with both chemotherapy and radiotherapy. There are several potential advantages to this approach. Malignant lymphocytes are highly sensitive to radiation and undergo apoptosis after exposure to relatively small doses. In addition, chemotherapy and radiotherapy work by different mechanisms so radiation may offer a way to address chemotherapy resistant disease. This is a critical point, because even though canine lymphoma is a chemotherapy responsive disease, it is not a curable. Virtually all dogs eventually fail because drug-resistant disease persists subclinically and leads to relapse, and the ability to overcome chemotherapy resistance would be a tremendous advance. Finally, the addition of radiotherapy could shorten the chemotherapy protocols currently used to treat canine lymphoma. This might have multiple positive effects, including slower development of chemotherapy resistance due to decreased tumor cell drug exposure; decreased cumulative chemotherapy toxicity; and, decreased cost and increased convenience for the pet owner.

These considerations lead several centers to incorporate radiotherapy into CHOP-based protocols for canine lymphoma. Sequential cranial and caudal half-body treatments were used to simulate a systemic treatment, since delivery of the full whole body dose would have fatal complications. Early reports were encouraging: at one institution, almost a third of dogs that received half-body radiotherapy were in remission and off therapy after two years. Several years later, results of the largest study published so far were somewhat less positive. Although the combination therapy was well tolerated, remission duration in dogs receiving half-body radiotherapy was only modestly improved at a median of 10 months. The authors of this study hypothesized that longer remissions were not achieved because the radiation dose was too low, because malignant lymphocytes survived by moving between body halves between treatments, or perhaps because some chemotherapy resistant lymphocytes were also radioresistant. However, they felt that more work looking at protocols combining chemotherapy and radiation was warranted. Unfortunately, data from these studies are now becoming available and despite initial reports they suggest that half-body radiotherapy provides little benefit compared to chemotherapy alone. Preliminary results from one study showed that dogs receiving half-body radiotherapy and chemotherapy had a median remission duration of only 7months. In a study conducted by the author, dogs receiving half-body radiotherapy had more gastrointestinal and hematologic toxicity, and more treatment delays. Use of this protocol has been discontinued.

After evaluation of available data it is difficult to recommend routine incorporation of half-body radiotherapy into CHOP-based protocols for canine lymphoma. Even though the theory and initial reports suggested a benefit, when the protocol was actually put into practice this benefit disappeared. This shows the importance of conducting carefully designed studies to fully evaluate new therapies before they are widely adopted. Additional work may identify a subset of dogs for whom half-body radiotherapy provides an advantage, but at the present time it appears that CHOP-based chemotherapy alone should remain the standard of care for canine lymphoma.

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ADVANCES IN OSTEOSARCOMA

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Osteosarcoma is the most common primary bone tumor in dogs and represents approximately 85% of all skeletal malignancies in this species. In dogs, it predominately affects large and giant breeds. Once a diagnosis of osteosarcoma is made treatment options generally fall in either of two categories: intent to cure or palliation. Intent to cure, although rarely attainable, usually involves control of the primary site via surgery (most often amputation) with adjuvant chemotherapy for metastasis. When curative treatment is not possible because of advanced metastasis, multiple primary lesions, or the inability of a patient to function adequately post amputation, palliation is a valid treatment goal. Palliation of bone pain may be accomplished with traditional opioid and non-opioid drugs, external beam radiation therapy, or non-cytotoxic chemotherapy.

In recent years, a number of important advancements have occurred that enhance our basic science and clinical understanding of osteosarcoma. Among them are a better definition of the metabolic abnormalities that occur, the expression of various genes and gene products, genome analysis, and clinically in the use of histologic grade, clinical stage, and bisphosphonate drugs.

Resting energy expenditure (REE), protein, and carbohydrate metabolism in dogs with osteosarcoma have been recently evaluated using the technique of dual-energy x-ray absorptiometry (DEXA) to determine total body, glucose flux, and rates of protein synthesis. A report comparing 15 weight-stable dogs with osteosarcoma with 12 control dogs found that the REE for dogs with osteosarcoma was significantly higher before and after surgery compared with the REE of healthy control dogs. In this study, dogs with osteosarcoma also had decreased rates of protein synthesis and increased urinary nitrogen loss and an increased glucose flux during the postoperative period. The clinical relevance of these findings includes the recognition that alterations in energy expenditure, protein synthesis, urinary nitrogen loss, and carbohydrate flux are similar to humans with cancer and that these findings are usually subclinical with affected dogs having no obvious clinical signs of cachexia.

Pathologic bone remodeling is an important part of the clinical presentation of osteosarcoma. The hypothesis of using surrogate indices of bone metabolism to help elucidate better diagnostic and therapeutic management of osteosarcoma inspired a study that evaluated excretion of N-terminal telopeptide (NTx) in urine as a marker for bone resorption. This study of 63 dogs with osteosarcoma when compared with 29 healthy age-matched controls found that dogs with appendicular osteosarcoma had significantly higher baseline urine NTx excretion than did the normal controls. In 17 dogs that had either amputation or standardized palliative therapies, significant reductions in urine NTx excretion were observed, suggesting that excessive bone resorption in dogs with osteosarcoma was probably linked with focal skeletal osteolysis or its consequences.

Histologic grade of osteosarcoma in humans and dogs can be a good indicator of prognosis. Recently a new histologic grading system for dogs has been proposed that is derived from histologic criteria of the degree of pleomorphism present, the number of mitoses/field, the tumor matrix, tumor cell density, percent of necrosis present, and tumor invasion into blood vessels. Histologic grade as it relates to survival is best determined by mitotic index and the degree of blood vessel invasion. Total and bone-derived serum alkaline phosphatase (ALP) activity is also predictive of survival. Therefore, dogs with high-grade tumors and elevated total serum ALP concentrations should be even more carefully evaluated for metastasis before starting adjunctive treatment protocols.

The observation that cancers of both humans and domestic species exhibit considerable heterogeneity in their clinical behavior and response to therapy despite having very similar/identical histologic appearance has promoted intense interest in developing ways to better subtype malignancies to better understand and predict their behavior and clinical outcome. The genomics revolution has provided valuable new tools and reagents to complement conventional histopathologic classification of malignancies.

The *p*53 gene encodes a nuclear phosphoprotein (p53) that acts as a tumor suppressor gene and it can have a central role in cell cycle kinetics and in carcinogenesis. The *p*53 gene recognizes damaged/abnormal DNA and either initiates repair processes or induces programmed cell death (apoptosis) if DNA damage is excessive. Absence of a functional *p*53 gene, p53 protein, or p53 pathway can remove a critical mechanism that normally stops the proliferation of transformed cells and disrupts apoptosis, and may ensure the development and progression of cancer clones. Mutations (alterations) of p53 have been found in 40% to 45% of cases of the ten most frequent cancers in humans, and alterations in p53 have been reported in many animal cancers. Abnormal p53 is frequently identified with immunohistochemistry. Normal (wild type) p53 is present in all cells, although usually in small amounts, and has a short half-life that makes it difficult to detect with immunohistochemistry. Therefore, detection of p53 in tumor specimens indicates alterations in the *p*53 gene or p53 gene product and indicates the presence of the tumor phenotype.

Overexpression of p53 can be detected at high levels in many human and animal malignancies including osteosarcoma and is predictive in humans. In dogs, p53 is being evaluated for predictive relevance also. A strong correlation has been demonstrated between canine p53 index (staining frequency and intensity) and clinical parameters such as tumor site, histologic grade and score, mitotic index, degree of tumor necrosis and pleomorphism. In addition, p53 index is reported to be higher in Rottweilers than in Great Danes and Terriers, confirming breed susceptibilities to osteosarcoma.

Ezrin is a gene that is associated with connecting the actin cytoskeleton to the cell membrane; it has recently been shown to be necessary for metastasis of osteosarcoma. High ezrin expression in canine osteosarcoma is associated with early metastasis and poor outcome.

Clinically, the standard of care of canine osteosarcoma still involves controlling the primary lesion (most often by amputation) and some adjuvant chemotherapy (most often cisplatin or cisplatin/doxorubicin) plus pain control as necessary. Amputation alone results in a median survival time of 3 to 6 months with a 1-year survival rate of 21% and all dogs die within 16 months. Amputation followed by chemotherapy increases the median survival to about 9 months with a 1-year survival rate of about 37%. Variations on this approach have been used for a long time and have been reported frequently. Adjuvant Immunotherapy following surgery has been reported in an experimental setting by Kurzman et al, who demonstrated that the administration of liposomal encapsulated muramyl tripeptide after surgery and chemotherapy resulted in a median disease free interval of 11.2 months. Likewise, another report of injecting a human cytotoxic T-cell line (TALL-104 cells) intravenously post surgery and chemotherapy resulted in a median survival of 11.5 months. Both of these experimental approaches provide significant advances over more traditional approaches.

Perhaps the most exciting advance in the treatment of osteosarcoma in dogs is the use of bisphosphonate drugs. Bisphosphonate drugs are now being incorporated into the standard of care for osteosarcoma in dogs. Although a number of drugs are currently available for clinical use in dogs, pamidronate disodium given intravenously has been reported on the most. Clinical experience and in vitro studies strongly suggest that bisphosphonate drugs like pamidronate disodium inhibit growth of osteosarcoma. A dose of 2 mg/kg pamidronate disodium diluted in 250 mL of sterile saline over 2 hours as a constant rate infusion every 28 days is advised for inhibition of osteolysis caused by tumor growth. This drug has also been shown to have some ability to mitigate bone pain associated with osteosarcoma.

Clinical stage is also an important predictor of survival. The presence of metastasis in patients with osteosarcoma signals clinical stage III. A recent study evaluating treatment responses in stage III dogs found that the median survival was 76 days (range 0–1583 days) and that dogs treated palliatively with radiation therapy and chemotherapy had the longest survival time (median survival 130 days) compared with dogs treated with surgery alone (median survival 3 days) or dogs treated with surgery and chemotherapy (median survival 78 days).

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TUMORS OF THE GI TRACT

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Tumors of the gastrointestinal tract (GI) occur in each of the different anatomic units from the oral cavity through the anus. They are varied histologically and clinical signs relate primarily to location, size, and the degree of compromise of normal function. Some are associated with multifocal localization and some are solitary lesions. Some authors include the liver and pancreas and perianal glands as part of the GI tract. Tumors of the GI tract have generally been adequately covered in a variety of formats. The purpose of this article is to update selected tumor types based on the latest literature available and explore some current controversies.

INFLAMMATORY BOWEL DISEASE (IBD) AND EPITHELIOTROPHIC LYMPHOMA IN CATS

Approximately 90% of lymphoma in cats is classified as intermediate- or high-grade based on histologic appearance. High-grade lymphomas are those with large amounts of cytoplasm, large and prominent nucleoli, hyperchromatic chromatin pattern staining, and numerous mitotic figures. Low-grade lymphoma is characterized by the presence of small lymphocytes with round nuclei, enough cytoplasm to result in relatively uniform spacing of nuclei, and mitoses are characteristically absent. High-grade tumors are sometimes referred to as "lymphoblastic" while low-grade tumors are sometimes referred to as "lymphocytic." Intermediate-grade tumors have characteristic between high and low-grade.

Inflammatory bowel disease in cats is associated with a lymphocytic (and often plasmacytic infiltration) of small reactive T lymphocytes. There has been speculation by pathologists and clinicians that lymphocytic–plasmacytic IBD in cats may actually represent a low-grade intraepithelial T-cell lymphoma and not a reactive infiltration by T cells. Epitheliotrophism in the context of alimentary lymphoma refers to the characteristic homing of neoplastic T cells to the mucosal epithelium of the intestinal tract. This form of lymphoma has been reported in both dogs and cats. With this variant of lymphoma the involved area is mostly infiltrated with small, and to a lesser extent a population of intermediate-size malignant lymphocytes, rather than larger lymphoblasts. Immunophenotyping will generally confirm the small lymphocytes as T cells in both epitheliotrophic lymphoma and IBD. Without the ability to preform clonal analysis, on the basis of morphology alone (which is all that routine H&E stained histopathology specimens can allow the pathologist to evaluate) it can be impossible to distinguish IBD from epitheliotrophic lymphoma. Clinicians need to be aware of this potential for confusion and for a misdiagnosis of IBD when in fact the clinical disorder is a rare variant of lymphoma. Because of this confusion, treatment for IBD will often precede the definitive diagnosis of lymphoma by many months. Cats with epitheliotrophic intestinal lymphoma usually have a predominance of duodenal lesions and have a prolonged clinical course.

The basis for the apparent relationship between IBD and lymphoma is unclear, but the presumption is that the IBD is the antecedent event leading to malignant transformation. There is abundant literature in human and veterinary medicine linking the effects of chronic inflammation to the development of cancer. In cats such inflammatory events as post-vaccination granuloma, eye trauma, and sunlight will precede malignant cancer in some individuals. Likewise in dogs, chronic wounds and chemical exposure may lead to cancer as well.

Perhaps the most widely accepted example of chronic inflammation preceding tumor development at the same site is found with chronic *Helicobacter* infection and gastric carcinoma. People that are colonized with *Helicobacter* are at dramatically higher risk for gastric cancer development than are uninfected people. Both dogs and cats with *Helicobacter* infections have been proposed as models of gastric tumor development in humans.

Non-epitheliotrophic lymphoma of the GI tract in cats is more often categorized as being high-grade. With high-grade lymphoma of the GI tract there may be associated mesenteric lymphadenomegaly, splenomegaly and/or hepatomegaly in addition to a specific intestinal localization. Non-epitheliotrphic intestinal lymphoma in cats is variably reported as being primary T-cell type and in other reports as primarily B-cell type and almost all will be FeLV test negative.

LARGE GRANULAR LYMPHOCYTE (LGL) LYMPHOMA

Large granular lymphocyte lymphoma is characterized by the presence of a morphologically distinct subset of lymphocytes that contain intracytoplasmic azurophilic granules. These cells are a normal, though minor, population of peripheral blood lymphocytes, but represent a large subset of intraepithelial lymphocytes in the intestinal tract. Most LGL lymphomas reported in dogs and cats are intestinal. In cats they are consistently found in the small intestine with a predominance of jejunal lesions. This disorder has a very aggressive clinical behavior and is usually of T-cell or non-B type origin; probably most consistent with natural killer (NK) cells. Interestingly, some cats that are diagnosed with LGL intestinal lymphoma have a history of a prior diagnosis (working or definitive) of IBD.

Some cats with LGL intestinal lymphoma will have nonspecific clinical signs such as anorexia, weight loss, vomiting and diarrhea. They frequently also have a palpable abdominal mass. Cats will also often have a circulating LGL lymphocytosis. Dogs with LGL intestinal lymphoma are often asymptomatic to paucisymptomatic when diagnosed with LGL malignant disease. In cats an associated leukemia with LGL lymphocytes is often reported. There are reports that alimentary lymphoma of all types in cats may be increasing in prevalence.

MAST CELL TUMORS OF THE GI TRACT

Mast cell tumors of the skin are very common but GI mast cells are far less common. Their full clinical characterization is also unclear. Miniature breeds of dogs, especially Maltese, appear to be most frequently affected. Affected individuals tend to be older (9.7 + 2.6 years) and no sex differences are apparent. The most common localization is the upper GI tract and the lumen of the associated gut is often narrowed.

Histologic features of this disorder are important to the clinician because confusion with GI lymphoma is possible. Mast cell tumors and lymphoma are both classified as round cell tumors. When mast cells have abundant cytoplasmic granules and are well differentiated confusion with lymphoma is unlikely. However, cases of T-cell GI lymphoma in dogs and GI mast cell tumors with very similar histologic features are reported. Tumor cells of lymphoma are characterized by round nuclei with dense chromatin, scanty cytoplasm and large distinct nucleoli. Mast cell tumors of the intestine have moderate to abundant cytoplasm with round to ovoid nuclei with sparsely scattered granules showing metachromasia. These granules, usually abundant in cutaneous mast cell tumors, are the hall mark of these cells but in intestinal tumors the granules may not be seen with routine H&E sections. These morphologic characteristics are very similar to those of moderate to large T-cell lymphoma of intestinal origin. In addition, variable eosinophilic infiltrations can be present in both lymphoma and mast cell tumors involving the gut. The use of immunohistochemistry, special stains like toluidine blue and alcian blue, plus the mast cell marker known as c-kit is vital for correct diagnosis.

There are limited reports of treatment of intestinal mast cell tumors. One reported dog was treated with lomustine (80 mg/m^2 orally every 3 weeks), prednisone (30mg/m^2 once daily x 7 days, then 20 mg/m^2 once daily x 7 days, then 20 mg/m^2 every other day). Supportive treatment with sucralfate and omeprazole were also given. This particular dog remained in partial remission for 7 months. In other reports, surgery followed in some cases by prednisone, vincristine, and/or cyclophosphamide resulted in very short periods of control (1 to 2 months at most).

INTESTINAL CHORISTOMA

A choristoma is a mass of histologically normal tissue that is found in an abnormal location. They are often classified by the predominant tissue within the lesion and further described by the location where the tissue if found. *Gastrointestinal choristoma* is the term for heterotrophic gastrointestinal tract tissue while *gastric choristoma* and *intestinal choristoma* refer specifically to lesions with only one type of epithelium. Choristomas are rare but they have been reported to involve the skin and subcutaneous tissues. They form following failure of separation between the notochord and a portion of the underlying endoderm during embryonic development. They typically are diagnosed in young animals.

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INTRACRANIAL TUMORS

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Intracranial tumors are well described in dogs and cats. The prevalence of this disorder is reported to be 14.5/100,000 dogs and 3.5/100,000 cats, although other reports indicate an incidence approaching 3% in dogs and slightly in excess of 2% in cats. In both species, meningioma is most common intracranial tumor and astrocytoma is the second most common. Choroid plexus and pituitary tumors are also relatively common and several other types are also reported (Table 1). The entire classification scheme for tumors of neurologic origin seems to be in flux. A number of recent manuscripts have addressed updates and changes to the current World Health Organization (WHO) classification. A variety of neoplasms metastatic to the brain have also been described.

Breeds most commonly identified in one large survey of dogs with primary intracranial tumors in descending order of frequency are mixed-breed dogs, Golden retrievers, Boxers, Labrador retrievers, German Shepherd dogs, Bull Mastiffs, and Rottweilers. The most common breed of cat reported in a different large survey were the domestic short hair followed by the domestic long hair. Affected individuals in both species are typically older (dog mean age 9.4 ± 3.4 years; cat mean age 11.3 ± 3.8 years).

Clinical signs are related to the specific intracranial localization, size, and compression of surrounding normal parenchyma, invasiveness, and inflammatory component of the tumor. Intracranial tumors are often slow growing so they are often diagnosed late in the course of the disease. Because growing tumors are confined by the calvaria, compression of adjacent normal brain parenchyma can contribute to clinical signs. Slowly expanding tumors give the brain time to accommodate to increased intracranial pressure and parenchymal compression. During the early stages of disease, clinical signs are often subtle and not dramatic. Later in the course of disease, the clinical signs most often associated with intracranial tumors in dogs are seizures, mentation change, vestibular syndrome, neck pain, vision loss, and occasionally regurgitation. In cats however, the most common sign is mentation change, followed by circling, seizures, ataxia, behavior change, vision loss, pacing and tetraparesis. A host of additional neurologic signs can be present in both species and frequently multiple clinical signs are present in the same individual.

Clinical evaluation of all patients suspected of having intracranial neoplasia should include basic clinical laboratory (complete blood count, chemistry profile, urinalysis), complete ophthalmic examination, neurologic examination, thoracic and abdominal radiographs (to look for metastasis to or from the brain) and some advanced imaging of the brain such as computed tomography (CT) or magnetic resonance (MR) imaging. Because of superior image contrast, MR is the preferred imaging modality for intracranial tumors. T1 and T2 weighted MR images are made during routine scanning and the information they contain is complementary. On T1-weighted images the cerebrospinal fluid (CSF) will appear dark (low signal intensity) and white matter will appear brighter than gray matter because white matter contains less water. The opposite is true on T2-weighted images where CSF appears white and gray matter has a higher signal intensity than does white matter. The signal intensity of the dura is low on both T1 and T2 in part because of its low water content. Tumors of the brain usually have a higher water content than surrounding normal brain so they usually appear hypointense on T1 images and hyperintense with T2 weighting. It is not always possible to distinguish intracranial tumors from other intracranial disorders such as infection with MR.

In one large study of MR images in cats with intracranial tumors found that the overwhelming majority of intracranial tumors in cats were meningiomas. In addition, meningiomas were always extra-axial (outside of the brain parenchyma) and were most often ovoid with marked contrast enhancement and peritumoral edema. Gliomas in this study were always intra-axial with ring enhancement and generally caused more peritumoral edema than other tumors.

Cerebrospinal fluid analysis can be helpful in distinguishing inflammatory from infectious from neoplastic disease. CSF analysis in canine cases of intracranial cancer is usually associated with elevated total protein, elevated white blood count, and a differential cytology characterized by mononuclear, neutrophilic, or mixed cell pleocytosis. However, these are nonspecific findings that are also compatible with other intracranial diagnoses such as granulomatous meningoencephalomyelitis (GME). Some individuals with intracranial tumors have normal CSF. For example, in one study only 39.6% of the cases of dogs with primary intracranial tumors had abnormal CSF.

Biopsy of intracranial tumors is standard of care in human medicine but it is rarely done antemortem in veterinary medicine. Obviously, biopsy is the only means of providing a definitive diagnosis but it is often not attempted because of financial constraints and potential patient morbidity. A number of different biopsy approaches have been described in dogs and cats but the one of most value and lowest morbidity is stereotactic CT-guided brain biopsy.

Loss or mutation of the p53 tumor suppressor gene occurs in about 33% of human astrocytomas, suggesting an early genetic event in tumorogenesis. An important consequence of loss of normal p53 activity is increased genomic instability, which appears to accelerate neoplastic transformation. The EGFR gene is the most frequently amplified oncogene in human astrocytic tumors. Over expression of p53 gene mutations and EGFR have also been identified in dogs with astrocytomas of different sub-types in a similar prevalence to that in man.

Glioblastoma multiforme (GBM) is a WHO grade IV astrocytoma and is the most common intracranial malignancy in people. The standard of care in humans with glioblastoma multiforme is surgical resection to the extent feasible and adjuvant radiation therapy plus chemotherapy that often involves temozolomide. This tumor type is uncommon in dogs but it has been reported and described in detail.

Treatment to remove the tumor mass and its secondary effects such as edema most commonly includes one or more of the following: surgery, chemotherapy, and radiation therapy. Successful treatment may also require concurrent suppression of seizures with anticonvulsants and the use of substantial doses of corticosteroids to reduce brain swelling. Humans with primary intracranial tumors are often treated with some combination of all three modalities.

An intact blood–brain barrier (BBB) can complicate the use of chemotherapy for intracranial tumors. Drugs given intravenously or orally may or may not reach the tumor. Different strategies exist to overcome the BBB including intra-arterial administration, barrier disruption, new ways of packaging drugs, and inhibiting drug efflux from the tumor. When chemotherapy is given intravascularly there is a common drawback in that the body acts as a sink and even under the best of circumstances, only a small portion of the administered drug reaches the tumor. Because of this, systemic toxicity is usually the dose-limiting factor. Drugs can also be given into the CSF (intrathecal administration) or directly into the tumor where 100% of the administered dose will be delivered to the target site. However, local delivery has variable and unpredictable distribution and concentration within the space into which it is distributed. In addition, local delivery's dose-limiting factor is neurotoxicity. Intravenous chemotherapy for brain tumors in dogs and cats is most commonly used and it primarily involves the use of Lomustine® (60 mg/m^2 orally every 6-8 weeks), Carmustine® (50 mg/m^2 IV over 20 minutes every 6 weeks) and occasionally cytosine arabinoside (600 mg/m^2 IV once a week). Concurrent use of prednisone and anticonvulsants (phenobarbital often plus potassium bromide) is usually required for successful management.

Temozolomide is a relatively new drug that is essentially an oral form of dacarbazine. Temozolomide is usually part of the standard of care of most brain tumors in people, but its use in veterinary medicine is uncommon. Very recently temozolomide use in a different context—rescue therapy for dogs with lymphoma—has been reported and suggests that it is well tolerated at an average dose of about 90 mg/m^2 daily for 5 consecutive days as part of a multi-drug protocol. Temozolomide may be a useful drug in the context of brain tumors in animals, but further investigation is required.

Surgery can be an effective treatment for meningioma if they are superficial enough. Obviously, only experienced neurosurgeons should attempt this but there are many veterinary neurosurgeons that routinely preform partial brain resection. Postoperative management can be intense but the prognosis in many cases is quite favorable. For example, postoperative survival for cats with meningioma is reported to be as long as 72 months assuming they survive the immediate postoperative period.

Radiation therapy for intracranial tumors can also be very rewarding. Radiation protocols vary among veterinary radiation oncologists but doses to the brain of 51 to 54 Gy given in 2.0 or slightly larger fractions are well tolerated. In a very recent report of 46 dogs with brain tumors (dose range 35 to 52.5 Gy) the median survival time calculated for deaths attributed to worsening of neurological signs was 1,174 days while the median survival time of all deaths attributed to disease or treatment consequences was 699 days (23.3 months). The use of computerized treatment planning systems and accurate positioning allows high doses of radiation (80% of total dose) to be limited to the gross tumor volume and the planning treatment volume. These advances allow for better tumor control with fewer side effects (radiation necrosis).

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Table 1. Histologic Classification of Intracranial Tumors in Dogs and Cats

Glial Cell Origin Astrocytoma Oligodendroglioma Oligoastrocytoma	Glial cell tumors are a varied group that pathologists may categorize by different schemes. New subtypes not included in the present WHO classification have been noted in dogs
Choroid Plexus and Ependyma Origin Ependymoma Choroid plexus papilloma Choroid plexus carcinoma	
Neuronal and Mixed Neuronal/Glial Cell Origin Gangliocytoma Ganglioglioma	
Embryonal Origin Olfactory neuroblastoma Medulloblastoma Neuroblastoma Primitive neuroectodermal tumor (PNET)	All embryonal origin tumors have been consolidated by most pathologists to a common term of PNET. PNETs are histologically indistinguishable from cerebellar medulloblastoma, but are found in other locations.
Meningeal Origin Meningioma	
Lymphoreticular Origin T- and B-cell lymphomas Histiocytic sarcoma Reticulosis	Classification of this group is confusing. Mass lesions may be singular or multiple. This group includes inflammatory subtypes that is part of the granulomatous meningoencephalomyelitis (GME) syndrome in dogs.
Pituitary Origin Adenoma Carcinoma	Often are considered to be secondary brain tumors because they affect the brain by means of local extension.
Other All other types are rare to very rare	

EXTRASKELETAL TUMORS OF BONE

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Bone in extraskeletal sites may be malignant (osteosarcoma) or benign (heterotrophic or ectopic bone formation; calcinosis circumscripta). Either may present as a boney mass associated with a soft tissue structure. Extraskeletal osteosarcoma clinically is very aggressive and survival is typically short, while benign mineralization has a much more favorable outcome.

Osteosarcoma in extraskeletal locations is rare in the dog. These tumors are bone-producing neoplasms of mesenchymal origin that lack any association with bone or periosteum. Extraskeletal osteosarcomas have been reported in cutaneous, mammary gland, muscle, gastrointestinal (GI) tract, spleen liver, thyroid gland, adrenal gland, urinary tract, reproductive, ocular, meningeal, and salivary gland tissues. Pathologists will typically use immunohistochemical techniques to further characterize tumor specimens and they often stain positive for vimentin confirming a mesenchymal origin.

The presumed pathogenesis for these unusual tumors is that they arise from resident populations of undifferentiated mesenchymal cells with osteogenic potential that are known as *inducible osteogenic precursor cells* (IOPCs). The IOPCs are different from committed or *determined osteogenic precursor cells* (DOPCs) of bone marrow origin. Both precursor cell types have multi-potentiality and possess the capacity to establish all marrow lines. The IOPCs are distinguished from DOPCs partly on initial dependency and continued persistence of appropriate microenvironment in the tissue. The microenvironment of cytokines (transforming growth factors β1 and β2), bone morphogenic proteins (BMP1, BMP2, and BMP3), BMP regulator proteins, and matrix proteins influence the continued activity and extent of bone formation. Transforming growth factors and related bone morphogenic proteins are especially important in inducing bone formation and stimulating differentiation of primitive mesenchymal cells into bone forming tissue.

A similar conceptual explanation may apply to extraskeletal osteosarcomas of cats such as vaccine-associated osteosarcomas and feline trauma-induced osteosarcoma of the lens. Both of these tumors develop in an environment characterized by chronic inflammation. Malignant transformation in these tumors is believed to be mediated by the favorable environment provided by the persistent activity of a number of inflammatory cytokines and growth factors that perpetuate metaplastic tissue formation and ultimately sarcoma formation.

Ectopic soft tissue mineralization that mimics bone is described by many synonyms in the literature including tumoral calcinosis, calcinosis cutis, tumoral lipocalcinosis, canine gout, hip stone, and calcinosis circumscripta among others. This syndrome has been reported in dogs and cats and other domestic and wild species of animals. Mineralization of soft tissues is generally classified into three types according to the underlying factors: dystrophic, metastatic, idiopathic, and iatrogenic calcinosis. Dystrophic mineralization occurs in patients with normal serum calcium and phosphate concentrations and the calcification is localized to specific areas of tissue damage. The primary lesion may result from trauma, inflammation, infection, necrosis, or neoplasia. Ectopic mineralization following sever inflammation have been reported with foreign body reactions, otitis externa, interdigital pyoderma, neoplasia, demodicosis, and similar conditions. Metastatic mineralization occurs in a clinical setting of hypercalcemia and/or hyperphosphatemia such as may be seen with chronic renal failure or vitamin D toxicosis. Idiopathic mineralization occurs in the absence of known tissue injury or metabolic abnormality. Iatrogenic mineralization typically arises secondary to a treatment or surgical procedure with calcification occurring at the site of invasion. One large retrospective study of ectopic soft tissue calcification found that repetitive trauma and injury can play a role in inducing this syndrome in apparently normal dogs.

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TUMORS OF THE HEART AND HEART BASE

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Tumors of the heart and heart base are uncommon in dogs and cats. Tumors of the heart can be both primary and metastatic lesions. In humans the frequency of tumors metastatic to the heart is estimated to be 20 to 40 times that of primary heart tumors which themselves occur with a reported incidence of between 0.0017% and 0.19%. The much higher prevalence of metastatic lesions to the heart has also been reported in veterinary literature. However, presumably because of their greater rarity there are more reports of primary cardiac tumors in dogs and cats than there are of metastatic types.

In dogs, hemangiosarcoma is reported to be the most common cardiac tumor. Almost all primary cardiac tumors involve the right side of the heart, especially the right atrium. Other histologic types are reported and include fibroma, fibrosarcoma, rhabdomyoma, rhabdomyosarcoma, myxoma, teratoma, lipofibroma, mesothelioma, granular cell, and others. Tumors of the heart that are located within the lumen of the cardiac chambers (intracavitary) as opposed to the wall or septa are especially uncommon.

Clinical features associated with these tumors are diverse even among tumors of similar size and similar location. Most cardiac tumors are located intrapericardially and cause pericardial effusion and cardiac tamponade that can restrict ventricular filling and result in venous compression and failure behind the heart and poor cardiac output. Some cardiac tumors (most often intracavitary location) do not cause pericardial effusion. Clinical signs in theses cases most often are secondary to congestive heart failure or low cardiac output by obstructing blood flow or thromboembolism. Tumors that extensively infiltrate the heart can lead to arrhythmia and/or to poor myocardial contractile function.

Pericardial effusion can be a sequela to tumors of the heart and heart base and is especially common with hemangiosarcoma and chemodectoma. Pericardial centesis is an essential part of the diagnostic evaluation when effusion is present, but it is often unrewarding in establishing a definitive diagnosis. Most tumors of the heart and heart base (lymphoma excepted) do not exfoliate well or often enough to provide markers for a specific tumor type.

A large survey of cardiac tumors in dogs (729,265 medical records queried) found that 46% of all cardiac tumors in dogs were hemangiosarcoma while 5% were aortic body tumors, and 2% were due to lymphoma. A large number of diagnoses in this retrospective multi-institutional study were simply coded as "tumor-heart" (34%) so their true identity was not available for analysis. Presumably some or most of these were metastatic types. Most affected dogs were older, with hemangiosarcoma being reported most commonly in all age ranges affected. Breeds of dogs at higher risk for developing cardiac tumors were the Saluki, French Bulldog, Irish Water spaniel, Flat-Coated retriever, Golden retriever, Boxer, Afghan hound, English setter, Scottish terrier, Boston terrier, Bulldog, and German Shepherd dog.

Tumors of the heart base arise either from aortic body or carotid body chemoreceptor organs and are collectively termed *chemodectomas* or *heart-base tumors*. Chemoreceptor organs are part of the parasympathetic nervous system and they are sensitive to changes in blood carbon dioxide concentrations, pH, and arterial oxygen tension. They can initiate changes in the depth and rate of respiration, minute volume, heart rate, and arterial blood pressure in response. Although some variation occurs, aortic bodies in dogs are usually located at the base of the heart near the origin of the coronary arteries; dorsal, ventral, and lateral to the aortic arch; between the aorta and the pulmonary artery; and near the root of the right subclavian artery. In cats the left aortic body is located at the base of the left subclavian artery and the right aortic body is located in the angle between the right subclavian and the right common carotid artery. Carotid bodies are located at the bifurcation of the common carotid artery. Most chemodectomas in dogs and cats are nonfunctional but cause clinical signs as a result of mechanical disturbances and space occupation. Tumors of the heart base appear to most common in brachycephalic breeds.

Diagnostic procedures include thoracic and abdominal radiography, electrocardiography, and echocardiography in addition to basic physical examination and clinical laboratory analysis. Echocardiography is especially useful to differentiate heart-base tumors from other cardiac tumors.

Treatment may be merely symptomatic or aggressive. For example, arrhythmias can be suppressed with medication, congestive heart failure can be managed with medication, and effusions can be drained to provide symptomatic relief. In cases of pericardial effusion, pericardectomy can provide relief and reverse heart failure from tamponade. In one study of heat-base masses, dogs that underwent pericardectomy had a mean survival time of 661 days +/- 170 days while dogs that were treated medically had a mean survival of 129 days +/- 51 days.

Surgical resection of the tumor when possible plus pericardectomy and adjuvant chemotherapy (doxorubicin based) was reported in 25 dogs with cardiac hemangiosarcoma and found a median survival of 43 days in dogs with right atrial disease treated by surgery alone, but a median survival of 118 days if the resection was limited to the right atrial appendage. If a doxorubicin-based chemotherapy protocol was given after surgery median survival was 175 days.

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IMMUNOTHERAPY IN THE TREATMENT OF CANCER OF THE BLADDER AND URETHRA IN DOGS AND CATS

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Transitional cell carcinoma (TCC) of the bladder and urethra is the most common neoplasia of the lower urinary tract in dogs and cats. It is often localized in the bladder neck area and extending into the urethra; therefore, surgical management would interfere with maintenance of bladder storage function and urinary continence. Furthermore, prognosis is poor due to malignant biological behavior. Currently, the administration of mitoxantrone and platin derivatives[3] or mitoxantrone and piroxicam[4] have been favored by oncologists in cases unsuitable for surgical management with median survival times (MST) of 358 days and 291 days, respectively. Local infiltration of canine and feline lower urinary tract carcinomas with the cytokine interleukin-2 (IL-2) has shown promising results in a pilot study[2] and has been used since by the author in selected cases. Anti-tumor activity of IL-2 against TCC may be the result of increased release of toxic granula by eosinophils.[1] We report the results of a retrospective analysis of a treatment protocol using local human recombinant IL-2 administration into urethral and bladder carcinomas by endoscopy or during ablative surgery and adjunctive oral meloxicam administration.

Thirteen dogs, four male and nine female, with a mean body weight of 17,2 kg and a mean age of 11 years presented with signs of hematuria and dysuria and various other inconsistent clinical symptoms were diagnosed to have TCC of the bladder (13 dogs) and urethra (7 dogs) by ultrasonography, cystoscopy and cytology or histology. Four of the dogs were staged worse than T1N0M0. Seven received endoscopically assisted infiltration of 9 million units of r-Hu IL-2 diluted in 2 mL glucose 5% solution and six dogs following surgical ablation of tumor tissue from the bladder neck area. Treatment was repeated in three. The same procedure was applied to four cats with TCC. Mean survival time was 310 days with clinical improvement in seven dogs; however MST was only 210 days in the dogs, while cats had a more favorable outcome of a MST of 375 days and clinical improvement in all cases. When divided by response rate, 40% of the dogs had a survival time (ST) longer than one year, while 54% had an ST shorter than 6 months. No factors related to response could be identified.

DISCUSSION

The relatively small number of cases did not allow demonstration of the benefit of surgical ablation of tumor tissue in order to minimize obstruction of the lower urinary tract and reduction of clinical signs. In the pilot study only the endoscopic approach had been used and was favored by the pet owners because of minimal invasive properties. However, rapid recovery and restoration of normal lower urinary tract function was reported by some of the owners of surgically treated dogs and cats and was the reason to ask for repetition of the procedure. The reasons why some of the dogs seemed to benefit from the treatment and others had such a poor outcome could not be identified.

The results suggest that local treatment with IL-2 injected into the tumor region by endoscopy or during ablative surgery could be useful in some dogs and in cats with TCC of the bladder and urethra.

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LYMPHOMA

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CLASSIFICATION OF LYMPHOMA

Lymphoma can be classified according to World Health Organization (WHO) clinical stage, anatomic site, histologic/cytologic phenotype, and immunophenotype.

Canine Classification

The multicentric form, typically WHO stage III or IV, accounts for the majority of cases (80 to 85%) in the dog. Alimentary (~7%), cutaneous (~6%), mediastinal (~3%), and miscellaneous extranodal forms (central nervous system, bone, heart, nasal cavity, primary ocular) are less frequently encountered. The majority (80%) of canine lymphomas are similar to medium- and high-grade non-Hodgkin's lymphoma in people. Approximately 70% to 80% of canine lymphomas are of B-cell immunophenotypic derivation, with the remainder being primarily of T-cell derivation.

Feline Classification

In the last 20 years, the availability of widespread feline leukemia virus (FeLV) testing and vaccination programs has resulted in a shift in the frequency of anatomic type, immunophenotypic derivation, and retroviral association in cats with lymphoma. Prior to this era, the mediastinal and multicentric forms predominated, and lymphoma was associated with younger, FeLV-positive cats. Today, lymphoma primarily affects older FeLV-negative cats and the alimentary form predominates. The majority of affected cats (80–90%) are negative for FeLV antigenemia. As one would predict, along with a shift away from FeLV antigen-associated tumors has come a shift away from traditional signalment and relative frequency of anatomic sites. The median age of 9 to 10 years now reported is considerably higher than the 4 to 6 year medians reported prior to this era. The median age of cats within various anatomic tumor groupings has not changed, and sites traditionally associated with FeLV (ie, mediastinal and multicentric) still usually occur in younger, FeLV-antigenemic cats, while the alimentary form occurs most often in older, FeLV-negative cats. Three distinct classes of lymphoma in cats, small cell lymphoma, large granular lymphoma, and Hodgkin's-like lymphoma, have more recently been described.

DIAGNOSIS

Palpation of all assessable lymph nodes, including a rectal examination in the dog, should be undertaken. The mucous membranes should be inspected for pallor or petechia indicative of anemia or thrombocytopenia. Abdominal palpation may reveal organomegaly, intestinal wall thickening, or mesenteric lymphadenopathy. Thoracic compression in cats and auscultation in both dogs and cats may suggest the presence of a mediastinal mass and/or pleural effusion. Funduscopic and ocular assessment may reveal abnormalities (eg, uveitis, hemorrhage, ocular infiltration).

Hematologic Abnormalities

A complete blood count (CBC) is a necessary part of any evaluation for lymphoma. Anemia, when present, is usually normocytic, normochromic (nonregenerative) reflecting anemia of chronic disease. Cats with FeLV-associated disease often have a macrocytic anemia. The anemia may be accompanied by thrombocytopenia and leukopenia and circulating atypical lymphocytes if significant myelophthises is present. Bone marrow aspiration is required for clinical stagingl; however, if a client wishes to treat irrespective of stage, bone marrow aspiration does not need to be performed.

Serum Biochemical Abnormalities

These may reflect the anatomic site involved (eg, liver-specific enzyme or bilirubin elevations may result from hepatic parenchymal infiltration). Approximately 15% of dogs with lymphoma (40% of those with mediastinal involvement) will have hypercalcemia secondary to a paraneoplastic syndrome.

Retroviral Status

Retroviral screening (ie, FeLV and feline immunodeficiency virus [FIV]) is important in cats from a diagnostic and prognostic standpoint.

Imaging

Imaging by radiography, ultrasonography, or computed tomography (CT) may be of diagnostic importance in those cases lacking peripheral lymphadenopathy or limited to intracavitary or extranodal sites. Imaging is equally important for clinical staging (ie, determining extent of disease), which may have a significant impact on the overall prognosis and alter the caregiver's willingness to pursue therapy. For the more typical cases of multicentric lymphoma in dogs, imaging in the author's practice is limited to thoracic radiographs as there is no prognostic difference between dogs with stage III versus IV disease (absence or presence of hepatic and splenic involvement). However, cranial mediastinal lymphadenopathy is of prognostic significance. Special studies, including contrast imaging of the gastrointestinal tract, CT, or myelographic studies of the central nervous system, and skeletal surveys are reserved for those cases where the appropriate anatomic site is suspected.

Cytologic and Histopathologic Diagnosis

Microscopic confirmation of lymphoma is the cornerstone of diagnosis in both the cat and dog. Cytologic evaluation of fine needle aspirates (FNA) by a skilled clinical pathologist may be adequate to make a diagnosis of lymphoma in dogs; however, conclusive histologic confirmation is recommended. For infrequent situations where the microscopic characteristics are inconclusive—that is, reactivity, early malignancy or low-grade malignancy cannot be differentiated—clonality by polymerase chain reaction (PCR) is now available at some centers and can be performed on cytology samples (either slide preparations or samples collected in cell media). Histologic and cytologic samples can be analyzed by various histochemical and immunohistochemical techniques to determine immunophenotype (B versus T cell).

In the cat, cytologic evaluation of FNA of lymph node is often not sufficient for diagnosis of lymphoma owing to difficulties encountered in distinguishing lymphoma from benign hyperplastic lymph node syndromes unique to the species.

PROGNOSIS

Prognostic Factors in Dogs

Most studies fail to correlate age, body weight or breed with prognosis. Clinical stage, with the exception of marked stage V disease, does not appear to significantly affect prognosis in dogs. The exception would include those cases where bone marrow is heavily infiltrated, where gross leukemia is present, or if peripheral cytopenias exist secondary to myelophthisis. Two factors that consistently correlate with prognosis in dogs are immunophenotype and WHO substage status. Dogs with CD3 immunoreactive tumors (ie, T-cell derivation) are associated with significantly shorter remission and survival durations. Similarly, dogs with substage 'b' disease (ie, clinically ill) also do poorly when compared with dogs with substage 'a' disease.

Prognostic Factors in Cats

Factors most strongly associated with a more positive outcome in cats are complete response to therapy (unfortunately this cannot be determined prior to therapy), negative FeLV status, early clinical stage, substage 'a,' and the addition of doxorubicin to the treatment protocol. In general, cats that are not FeLV antigenemic and who achieve a complete response on combination-based chemotherapy protocols have a higher likelihood of long-term survival, with approximately one third surviving one and a half years after diagnosis. Cats with nasal lymphoma, overall, have the best prognosis, as local radiotherapy (or chemotherapy if radiotherapy is not available), results in excellent control with median survivals approaching 1.5 years.

THERAPY

The management of lymphoma in companion animal species can be quite gratifying initially as response rates approaching 90% in dogs and 60% to 70% in cats result following a variety of chemotherapeutic approaches. Unfortunately, most animals will eventually succumb to disseminated relapse of their disease in a more chemotherapy resistant form. Once a diagnosis is established, untreated dogs and cats will generally live an average of 4 to 6 weeks. Lymphoma, typically a systemic disease, requires a systemic approach to therapy (ie, chemotherapy). Exceptions to this include cases of solitary site or extranodal lymphoma where local therapy involving either surgery or radiotherapy may be indicated.

Systemic Chemotherapy in Dogs with Lymphoma

A variety of chemotherapeutic approaches have been reported in the veterinary literature for the treatment of lymphoma. Prior to initiating therapy, caregivers should be educated as to the advantages and disadvantages of several chemotherapy protocols. Several factors should be considered and discussed, including the cost, time commitment involved, efficacy, toxicity, and the experience of the clinician with the protocols in question.

Combination protocols used in veterinary practice are usually modifications of CHOP protocols initially designed for treating people with lymphoma. CHOP represents combinations of cyclophosphamide (C), doxorubicin (H, hydroxydaunorubicin), vincristine (O, Oncovin®), and prednisone (P). Regardless of which CHOP-based protocol is used, overall median remission and survival times are approximately 8 and 12 months, respectively. Approximately 20% to 25% of treated dogs will be alive 2 years or longer after initiation of therapy. Most modern treatment protocols end chemotherapy after approximately 4 months and after therapy is discontinued, dogs are reevaluated monthly by physical examination with special attention to lymph node size.

Doxorubicin represents the most effective and commonly used single agent chemotherapy protocol available for dogs with lymphoma. Doxorubicin (30 mg/m^2, IV, q 3 weeks) is given every 3 weeks for a total of five treatments. In dogs weighing less than 15 kg and cats, the dose of doxorubicin used is 1 mg/kg. While cardiotoxicity is the dose-limiting toxicity (DLT) in dogs, renal toxicity is the DLT in cats and creatinine and urine specific gravity should be monitored in the cat to ensure safe levels for doxorubicin delivery. Response rates of 75% to 80% result and median remission and survival durations of 5 and 7 months, respectively, are reported for single agent doxorubicin in the dog. Advantages of this single agent protocol include less cost, a shorter time commitment, fewer hospital visits, and side effects that are attributable to one drug.

Alternatives should be offered to caregivers who, for financial or other concerns, decline more aggressive systemic chemotherapy. In these cases prednisone (2 mg/kg, PO, daily) will often result in short remissions of approximately 1 to 2 months. It is important to educate these clients that dogs receiving prior prednisone therapy are more likely to develop multiple drug resistance and experience shorter remission and survival durations with subsequent combination protocols should more aggressive therapy be pursued. This is particularly true if prednisone has been used long-term or if dogs have experienced a recurrence while on prednisone. Therefore, the earlier clients opt for more aggressive therapy, the more likely a durable response will result.

Systemic Chemotherapy in Cats with Lymphoma

In general, cats do not experience as high response rates or remission and survival durations as dogs with lymphoma; complete response rates are between 50% and 70%, and overall median remission and survival durations are approximately 4 and 6 months, respectively. This is tempered somewhat with the knowledge that a larger proportion of cats (30% to 40%) that achieve a complete response with combination chemotherapy experience more durable (ie, ≥2 years) remission and survival times than do dogs. The response rate and length of response vary according to the presence or absence of prognostic factors discussed previously. CHOP-based protocols are preferred by the author for cats.

For cases of “small cell” lymphoma in cats (eg, GI and hepatic) a protocol combining chlorambucil (20 mg/m^2 PO every 2 weeks) and prednisone (5 mg/day) is usually highly effective and results in long-term remissions.

Reinduction or Rescue Therapy

Unfortunately, most dogs and cats with lymphoma experience a relapse of their disease following initially successful chemotherapy. At the first recurrence, it is recommended that reinduction be attempted by restarting the induction protocol that was initially successful. The likelihood of a response and the length of the response are, in general, half that encountered in the initial therapy; however, a subset of animals will enjoy long-term reinduction.

If reinduction fails, the use of so called “rescue” agents or protocols may be attempted. Rescue agents are drugs or drug combinations that are not found in the standard CHOP protocol and are specifically withheld for use in the drug-resistant setting. The most common protocols include single agent or combination use of CCNU, actinomycin D, mitoxantrone, and MOPP (M, mechlorethamine; O, Oncovin®; P, procarbazine; P, prednisone). Mitoxantrone, doxorubicin, and MOPP have also been advocated in cats with resistant relapse. Overall rescue response rates of 40% to 50% are reported; however, most responses are not durable with median durations of 1.5 to 2 months being the norm. A small subset of animals will enjoy longer rescue durations.

Therapy for Extranodal Lymphoma

If extranodal involvement is part of a multicentric disease process then systemic therapies previously discussed should be instituted. However, if the extranodal site is solitary and not part of a multicentric presentation, local therapy may be performed without institution of systemic chemotherapy. In these cases strict adherence to staging diagnostics, including bone marrow evaluation and radiographic/ultrasonographic imaging of the thorax and abdomen, are warranted to ensure the process is localized.

ALLEVIATING ADVERSE EVENTS FROM CHEMOTHERAPY

Breed Predisposition to Adverse Effects of Chemotherapy

Certain breeds, in particular collies, are known to be at risk for toxicity from chemotherapeutics that are actively transported by the p-glycoprotein pump (eg, vinca alkaloids, epipodophyllotoxins, anthracyclines, dactinomycin, and the taxanes). These breeds have a high frequency of a pharmacogenetic mutation of the MDR1allele. If a dog is homozygous for the mutant allele, they will be affected and at risk; if they are heterozygous for the mutant allele, they are a carrier. A clinically relevant PCR assay (performed on cheek swabs) for the mutant status is available through Dr. Katrina Mealey’s group at the Washington State University Veterinary School. It is recommended that if you are contemplating treating a breed at risk, non-p-glycoprotein substrate chemotherapeutics (eg, alkylators) be substituted in protocols until the results of the analysis are available (turnaround time of approximately 1 week).

Gastrointestinal (GI) Toxicity

Gastrointestinal (GI) toxicity may be secondary to direct damage to intestinal epithelial cells or via efferent nervous stimulation of the chemoreceptor trigger zone (CRTZ). It typically manifests as inappetence, nausea, vomiting, and/or diarrhea beginning 3 to 5 days after therapy. When direct stimulation of the CRTZ is responsible, vomiting is maximal on the day of therapy (eg, when using cisplatin). The consequences of significant gastrointestinal adverse events are several-fold and include dehydration, nutritional deficiency, delay of subsequent therapy, dose reduction, financial burden (ie, hospitalization), and diminished client enthusiasm for continuation. The judicious use of antiemetics and antidiarrheals is recommended. If an animal has had significant gastrointestinal events following a particular chemotherapy, sending the client home with 3–5 days of prophylactic therapy is indicated. The most effective class of antiemetics in people undergoing chemotherapy are the NK-1 receptor antagonists; Cerenia® (maropitant; Pfizer Animal Health), which recently received FDA approval for use in dogs is a superior antiemetic in dogs receiving chemotherapy and has several advantages over off-label antiemetics used in the past. It is important to keep in mind that most side effects of chemotherapy are self-limiting and will resolve with minimal veterinary intervention. Most clients are able to perform the nursing care required to support animals through GI side effects. Typically, dose reductions of 20% are recommended for severe gastrointestinal toxicity at the time of the next scheduled treatment. Dose reductions should not be contemplated lightly as dose intensity is extremely important for antitumor response; therefore, if adverse effects can be abrogated by symptomatic treatments (antiemetics, antidiarrheals) rather than dose reduction, this should be attempted first.

Myelosuppression

Myelosuppression is secondary to damage to the rapidly dividing bone marrow stem cells. Cells with the shortest circulating life span are most susceptible; therefore, myelosuppression is most commonly manifested as a decrease in neutrophil and/or platelet counts. Specifically, chemotherapy treatment should be delayed with a neutrophil count of ≤1500 to 2000/µL or a platelet count of ≤50,000/µL. The exception to this rule is if the cytopenia is believed to be secondary to the tumor, either a paraneoplastic syndrome or from myelophthisis. In either case, treatment of the neoplasia is needed to resolve the low cell count. Moderate (≤1000 neutrophils/µL) myelosuppression in an otherwise clinically normal animal can usually be managed with prophylactic oral antibiotic administration and body temperature monitoring. Repeating the neutrophil count in 5–7 days generally will reveal marrow recovery. The use of human hematopoietic growth factors is controversial and rarely necessary in veterinary-based protocols. If the myelosuppressed animal is ill, or pyrexic, hospitalization with broad-spectrum parenteral antibiotics, fluid support, and careful observation are indicated. Hunting for a source of infection (eg, occult pneumonia, urinary tract infection, or sepsis) may be indicated if clinical signs do not rapidly normalize with broad-spectrum antimicrobials and fluid support. Typically, dose reductions of 20% are recommended if the neutrophil count falls below 500/µL at nadir, or below 1500/µL at the time of the next scheduled treatment. Dose reductions should not be contemplated lightly as dose intensity is extremely important for antitumor response.

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AGING WELL: HOW THE SCIENCE OF AGING INFORMS THE PRACTICE OF WELLNESS

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Why do we age? What are the genetic and non-genetic determinants of exception longevity? If cancer is indeed the product of time-related accumulation of genetic damage, then why are the oldest-old cancer resistant? The goal of this article is to illustrate how investigative efforts to answer these and other questions relevant to the biology of aging will eventually provide clinicians with best practice guidelines to promote healthy longevity.

UNDERSTANDING THE AGING PROCESS

Not all organisms undergo senescence at the same tempo. Dogs and humans exhibit gradual senescence (deterioration over years to decades), whereas other species, such as bamboo, have very rapid senescence (deterioration over days). There is an eclectic group of organisms that exhibit negligible senescence; age-related deteriorative changes are virtually imperceptible in these species. Not surprisingly, organisms with negligible senescence, including rockfish and bristlecone pine, are currently the subject of great scientific interest.

Understanding the mechanisms of organismal senescence and how morbidity can be compressed, culminating in an extension of healthy life span, is the goal embraced by most biogerontologists. It is important that these aims be clearly articulated to the public. It is also critical that the public understands what are not the goals of biogerontology research. For example, reversal of aging and achieving immortality are not considered tenable objectives.

Lessons From Evolutionary Biology

It has been argued that longevity—not aging or senescence per se—is under genetic control. These so-called longevity genes extend longevity by increasing physiological reserve or increasing disease resistance, rather than having a direct effect on the intrinsic rate of aging. Evolutionary biologists would concur that genes, which regulate late-life deterioration, would not be under the influence of natural selection. Instead, natural selection favors genes that influence the likelihood of reproductive success, because organisms rely upon the successful completion of development and reproduction to perpetuate the species. During the post-reproductive period, however, the force of natural selection quickly diminishes, rendering organisms ill equipped to protect themselves against the age-related accumulation of molecular damage. Seldom is this an important consequence to animals living in the wild, because in general, they experience relatively brief post-reproductive life spans owing to their vulnerability to predators, accidents, or infectious diseases. In contrast, dogs, humans, and other highly protected domesticated animal populations do encounter the manifestations of organismal senescence, including the development of cancer and other age-related degenerative diseases.

When it comes to age-related deterioration and disability, at least two tenets of evolutionary theory would suggest that humans, dogs and other domesticated species are indeed hard-wired for post-reproductive calamity. First, the Disposal Soma Hypothesis states that after reproduction, the soma (body) can be thrown away. Second, genes that confer an advantage early in life may also exert detrimental effects in the post-reproductive period—the Theory of Antagonistic Pleiotropy. The incidence of several age-related diseases is likely to be under the control of such antagonistically pleiotropic genes. For example, genes that stimulate abundant blood vessel formation within the placenta (favoring successful reproduction early in life) might be considered detrimental later in life because they would promote a rich supply of blood vessels to rapidly growing tumors. Moreover, it is expected that the frequency of alleles that exert these late life detrimental effects would be maintained or even increased in the population, owing to their early-life benefit.

In his famous treatise, "An Unsolved Problem of Biology," Nobel laureate Sir Peter Medawar noted that in order to understand the consequences of senescence and age-related diseases, one would have to study the aging process of "protected" species. In a classic thought experiment, in which Medawar considered the aging of glass test tubes, he pointed out that in order to observe the consequences of aging, test tubes would have to be "domesticated"—that is, kept sheltered from damage in a little box so they would not suffer early "death" by rolling off of the laboratory bench.

Thus, organismal senescence and accompanying age-related diseases is an inevitable by-product of domestication. An organism is not built with any regard for optimizing aging. Instead, an organism is designed to successfully and advantageously complete its maturation and reproduction. As a consequence, one expects to see an accumulation of molecular disorder in species, which attain a prolonged post-reproductive life span. This progressive increase in molecular disorder leads to organismal senescence—physiological deterioration, an increased risk for age-related diseases, and an increased mortality rate.

Lessons From Studying the Oldest-Old

Centenarians—people who live to be 100 years—provide a potentially valuable "natural experiment" of highly successful aging. To date, the search for specific environmental exposures or lifestyle factors (eg. diet, education, physical activity) that confer an increased likelihood of living to 100 years has not been fruitful. Among centenarians, females outnumber males by more than 2:1. Among women, successful late reproduction—live childbirth at 40+ years—is a strong predictor of exceptional longevity. Larger particle size of high and low-density lipoproteins and higher plasma antioxidant capacity have also been associated with exceptional longevity in humans.

Siblings of centenarians are 15 times more likely to live to 100 years compared with the general population. The sustained mortality advantage seen in siblings of centenarians is observed throughout the life course, suggesting that their good fortune may be more strongly influenced by genetic than by environmental factors. A few genes in humans have already been implicated as candidate "longevity enabling genes" because the "bad" polymorphic variants of these genes are underrepresented in centenarians. These bad variants include the apolipoprotein E∊4 allele and the angiotensin-converting enzyme D allele. Genetic linkage analysis has provided evidence that a gene or several genes on human chromosome 4 significantly contribute to exceptional longevity. It should be noted that the genetic factors that contribute to exceptional longevity might be different from the genetic determinants of *average* life span.

Centenarians outlive the lot of us, but just how healthy are centenarians? When it comes to vulnerability to major age-related diseases, a recent study of lifetime medical histories suggests there are three flavors of centenarians: (1) SURVIVORS—those individuals with onset of at least one major disease prior to 80 years of age; (2) DELAYERS—those individuals who are free of all major diseases until after 80 years of age; and (3) ESCAPERS—those individuals who are free of all major diseases until after 100 years of age. This important study confirmed that centenarians are indeed a highly heterogeneous population—38% SURVIVORS, 43% DELAYERS, and 19% ESCAPERS. However, one can conclude that significant disease resistance is a characteristic of many centenarians; in fact, more than 60% of centenarians remained free of all major diseases until after the median age at death for their birth cohort. Our analysis of exceptional longevity in pet dogs reached a similar conclusion—76% of the oldest-old dogs delayed the onset of major diseases, and more than half of extreme aged dogs had profound disease resistance (ie, ESCAPERS). Interestingly, men and women may follow different trajectories to achieve exceptional longevity—male centenarians are less heterogeneous and healthier than female centenarians are.

Undoubtedly, exceptional longevity is a complex trait reflecting genetic, environmental, and stochastic (chance) influences. Based upon our current understanding of extreme aged humans and pet dogs, we posited that disease resistance is the central and essential determinant of exceptional longevity. In the extreme aged, disease resistance may be manifested as disease avoidance, delayed onset of clinical disease, or decreased mortality from specific diseases. High physiologic reserve likely contributes to exceptional longevity, because it may delay the clinical onset of diseases or ameliorate the deleterious effects of co-morbid conditions. Although counterintuitive, it remains unproven whether an individual's intrinsic rate of aging is a significant determinant of exceptional longevity. To date, there are no definitive data from dogs or humans supporting the hypothesis that a slow rate of physiologic decline is essential to achieving exceptional longevity. Future studies that collect longitudinal data on an array of age-sensitive physiologic parameters (eg, muscle strength, cardiovascular compliance, neurologic processing, inflammation/immune response) are needed to determine whether individuals reaching extreme age demonstrate a significantly different rate of physiologic decline than individuals with usual longevity. The compressed life span of dogs compared with humans could make such studies feasible in pet dogs.

THE COMPLEX RELATIONSHIP BETWEEN AGING AND CANCER

The association between aging and cancer is compelling enough for one author to formally consider gerontology as oncology. Conceptually, the association between aging and cancer can be dichotomized into: (1) the influence of aging on cancer risk; and (2) the influence of aging on the biological behavior of resultant cancers.

In humans, the risk for most adult-onset cancers increases dramatically with increasing age. For 12 major human cancers, more than 50% of cases are diagnosed in elderly individuals over 65 years of age. Experimental evidence also supports the hypothesis that a host's susceptibility to develop cancer is age-dependent. In an important study by McCullough and colleagues, young (3- to 9-month-old) and old (18- to 24-month-old) rats received implantation of cancerous rat epithelial cells into their liver. On day 7 after tumor cell implantation, the incidence of tumors in both young and old rats was 100%. However, on day 85 post implantation, all of the tumors had regressed in young rats, while tumors were present in 17 of 19 (89%) old rats. The striking age-dependent regression of experimental liver tumors in this study clearly demonstrates that an old host provides an environment that is in some way better suited for the survival and proliferation of tumor cells.

A recent study of transgenic mice suggests a previously unexpected relationship between cancer risk and aging. Mice over expressing the tumor suppressor gene, p53, showed profound tumor resistance, but protection against tumors was *not* associated with increased longevity. Unexpectedly, these mice had shorter lives than wild type mice because they had earlier onset of age-related deteriorative changes (eg, diminished muscle mass, dermal thinning, scoliosis). These results are consistent with the hypothesis that tumor suppression in mammals comes at a cost—an accelerated rate of aging.

Data from humans and dogs suggest that host age may influence the biological behavior of malignant tumors. It has been observed that certain tumors behave more aggressively in young adults, in contrast to the more indolent clinical course of these tumors in elderly hosts. For example, more than 50% of stomach cancers in young people (30—39 years old) are poorly differentiated (poor prognosis), whereas fewer than 5% of stomach cancers affecting people over 85 years of age are poorly differentiated. Our data show that the youngest dogs that develop prostate cancer are almost 7 times more likely to have skeletal metastases at the time of prostate cancer diagnosis than the oldest dogs that develop the disease.

Although cancer is a disease strongly associated with aging, age-specific cancer mortality rate in humans actually *declines* in the tenth decade of life. Indeed, scientists who study centenarians have uncovered a puzzling paradox—the oldest-old humans seldom develop lethal cancers. Studies in our laboratory suggest a similar decline in the percentage of extreme aged dogs that succumb to cancer. Taken together, this raises the possibility that cancer resistance genes are overrepresented in the oldest-old, where they may influence longevity by protecting old tissues from the development of life-threatening malignant tumors. At present, the precise nature of the apparent cancer resistance in the oldest-old is poorly defined at the tissue level, because few autopsy studies have been performed.

APPLYING A LIFE COURSE PERSPECTIVE TO AGING AND WELLNESS

It makes good sense to apply a life course perspective to studying the determinants of life span. Biogerontology should not be confined to the study of old cells, old dogs, or old people. The origins of many adult health outcomes are shaped significantly by early life events and experiences. For example, the risk of older people to suffer pathologic bone fractures secondary to osteoporosis is strongly dependent upon the peak bone mass established in the second and third decades of life. Similarly, we have shown that Rottweilers that undergo ovariohysterectomy or castration before 12 months of age have a 2- to 3-fold greater risk of developing osteosarcoma as adults compared with dogs that remain sexually intact throughout their lifetime.

Clearly, there are many unresolved questions relevant to the question of why do we age. Today, it is imperative that veterinarians and other scientists take an active role in shaping public dialogue on the goals of aging research—the compression of morbidity and extension of healthy life span.

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CORNEAL ULCERS

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CORNEA

The cornea is the most powerful refractive surface of the eye; it supplies 70% of the eye's refractive or light bending power. The cornea is also an extremely strong tissue. It is transparent so that light rays can enter the eye. Transparency is maintained by several anatomic mechanisms: 1) lack of blood vessels; 2) lack of pigment; 3) nonkeratinized anterior surface epithelium; 4) precise organization of the stromal fibrils; 5) small size of the stromal fibrils; 6) relatively dehydrated compared with sclera.

Most domestic animal species have four corneal layers. The outermost stratified squamous epithelium has three cell types (superficial squamous cells, wing cells, and basal cells). This layer is a barrier to the precorneal tear film. A basement membrane is secreted and attaches to stroma. The stroma constitutes approximately 90% of the corneal thickness, and it is relatively acellular (mostly collagen). Descemet's membrane is the basement membrane secreted by the corneal endothelium. It is produced throughout life, and therefore the thickness increases with age. It is about 14 µm thick! The innermost endothelium is only one cell layer thick, and contains a sodium ATPase pump. This feature is very important in maintaining corneal transparency, as the pump helps to keep the stroma relatively dehydrated.

Most of the corneal nerves are concentrated superficially. They are branches of the trigeminal nerve, and form a very dense anterior sensory neural network. The cornea is actually one of the most sensitive tissues in the body. There are no nerves in Descemet's membrane. The corneal thickness varies by species. It is often thinner centrally than peripherally, depending on the species.

The average thickness of the central dog and cat cornea is 0.6 mm; in the horse, the central cornea is approximately 1 mm thick.

ULCERATIVE KERATITIS:

The Most Important Disease of the Cornea

Ulcerative keratitis (corneal ulceration) means that the corneal epithelium and possibly varying amounts of underlying corneal stroma are missing. In simple traumatic corneal injuries in which a small amount of epithelium is absent, healing is rapid. Normal corneal epithelium is a very effective barrier against invading bacteria. If the ulcer becomes infected or the epithelium is unable to attach to the underlying stroma, healing is delayed.

In chronic or infected ulcers, proteases and collagenases digest protein and collagen of the stroma and may greatly speed the progression of an ulcer to a descemetocele, rupture of the cornea, and then to iris prolapse (within 12 to 48 hours in some cases).

Corneal dissolution and liquefaction under the influence of proteases is often referred to as "melting." Ulcers in which proteases are active have a grayish-gelatinous liquefied appearance around the ulcer margin which must be distinguished from corneal edema.

Ulcerative keratitis is the most serious ocular disease for veterinarians. Regardless of the initial cause, all ulcers have the potential to progress to endophthalmitis if not treated.

CLASSIFICATION/CHARACTERIZATION OF CORNEAL ULCERS

Depth

Superficial ulcerations or abrasions should heal rapidly if they do not get infected. They can be traumatic in origin. It has been shown that normal horse corneal epithelium migrates at 0.6 mm per day; it is assumed that the rate in the dog and cat is similar or faster.

Etiology

There are multiple causes of corneal ulcers. Corneal ulcers can result from mechanical causes such as traumatic abrasion; corneal or eyelid foreign bodies; and eyelid anomalies (entropion, distichia/distichiasis, ectopic cilia, and trichiasis)

Infectious etiologies also cause corneal ulcers. Infectious organisms can be bacterial, fungal, or viral. Culture and sensitivity are important diagnostic tools to use with infectious ulcers.

Keratoconjunctivitis sicca (KCS or “dry eye”) can result in corneal ulceration. This is especially true with cases of acute onset KCS, in which corneal ulceration can occur rapidly and progress quickly. Ulcers are less common with chronic KCS.

Bullous keratopathy results in rupture of epithelial bullae that form with chronic corneal edema. Ulcers result from the rupturing of the bullae. These ulcers can range in size from small to very large and are variably painful. This is a devastating disease in the cat.

Exposure keratitis can result from either neuroparalytic disease (facial nerve paralysis, resulting in an inability to blink) or from neurotrophic disease (paralysis of ophthalmic branch of trigeminal nerve; corneal sensation is important to healing of corneal ulcers).

DIAGNOSIS OF CORNEAL ULCERS

Clinical Signs

The majority of animals with corneal ulcers present with pain as evidenced by blepharospasm. Corneal sensation is one of the major protective factors that the eye exhibits. Corneal sensory nerves are located mostly in the superficial cornea, and the nerves lose their myelination as they cross from the periphery into the center of the cornea. An “axon reflex” is thought to exist in the cornea such that when corneal touch and pain receptors are stimulated, miosis of the pupil, hyperemia, and increased protein levels in the aqueous humor occur. The axon reflex is responsible for the clinical signs of anterior uveitis observed with painful corneal conditions. These results appear to be mediated by prostaglandins, histamine, acetylcholine, and possibly substance P. Other clinical signs seen commonly with corneal ulceration include epiphora, photophobia, and corneal edema, causing a change in transparency.

Diagnostics

Culture and sensitivity should be performed routinely when an ulcer is infected or "complicated." Not all small animal ulcers need to be cultured the first time you see the patient. However, if the corneal ulcer appears to be "melting" or if the ulcer has not responded to proper treatment, these ulcers should be cultured.

Schirmer tear test and/or phenol red thread test should be performed on all canine patients presenting with corneal ulceration. A large percentage of dogs with dry eye with initially present with corneal ulceration. An eye with an ulcerated cornea should have excessively high tear production resulting in epiphora. If the Schirmer tear test value is in the normal range or similar to the normal fellow eye, then KCS should be suspected.

Cytology can be performed using topical anesthetic. Remember to collect culture samples and perform Schirmer tear tests prior to applying topical anesthetic, as the anesthetics can interfere with interpretation of results.

ALL ulcers should be stained with fluorescein and sometimes with rose bengal. Fluorescein stain (which is hydrophilic) will adhere to exposed stroma, but will not stain epithelium or Descemet's membrane. Rose bengal is used to evaluate mucin tear layer defects, and devitalized epithelium that is still attached but not healthy.

TREATMENT OF CORNEAL ULCERS

There are multiple steps in the treatment of a corneal ulcer. The deeper the ulcer, the more aggressive is the medical and likelihood of surgical therapy. The first step is to determine the etiology, and remove or eliminate the specific cause. This means evaluating the eyelids and eyelashes, tear production, corneal culture, and corneal cytology.

Broad-spectrum antibiotics are usually administered; culture and sensitivity tests can guide selection in recurring, nonhealing, or infected ulcers. Triple antibiotics, chloramphenicol and tobramycin are safe antibiotics in dogs, while gentamicin, cefazolin, and ciprofloxacin are very irritating in noninfectious situations.

Prevention of collagen breakdown and ulcer progression are also important steps. Collagenases and proteases are derived from leukocytes in the tears and can be powerful in the destruction of corneal stroma. There are several drugs that can be used to help inhibit protease activity:

ANTIPROTEASES

Serum contains an alpha-2 macroglobulin with anticollagenase activity. Blood is drawn from the patient or an animal of the same species, spun down, and serum drawn off and stored in the refrigerator in a dropper bottle or serum tube for up to 7 days. It should not be stored at room temperature, but the dose about to be given can be warmed to room temperature immediately before administration. Serum is nontoxic, and should be used as many times a day as possible. EDTA (0.17%) can be given several times a day as well.

Acetylcysteine (5%) is used topically for its collagenase and protease inhibiting properties. Acetylcysteine is unstable at room temperature, so the solution must be kept refrigerated. Frequency of treatment is decreased from every 1 to 2 hours for the first few days to three or four times daily for the next 7 to 10 days.

Treatment of accompanying anterior uveitis is also important with corneal ulceration. Topical 1% atropine is usually instituted to relieve ciliary spasm and pain (cycloplegia) due to secondary anterior uveitis, and to decrease the formation of synechiae from the miotic pupil (as a result of uveitis). Be careful as it can cause a temporary KCS in small animal patients. Topical nonsteroidal anti-inflammatory drugs (NSAIDs) can be used to treat ulcer-induced uveitis in some cases.

In the treatment of deep corneal ulceration and descemetoceles, provision of corneal support is often important. Coverage with one of the various kinds of conjunctival flaps should be maintained for 10 to 21 days. Types of conjunctival flaps include 360 degree, hood, island, pedicle, and bridge.

A MEDLEY OF FELINE OPHTHALMIC DISEASES

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Four common ocular feline diseases are summarized below. The lecture itself is "a day in the clinic" presentation discussing several case histories for each of the eight diseases.

FELINE HERPETIC KERATITIS

The same feline herpes virus (FHV-1) that causes rhinotracheitis in cats causes three ocular syndromes: ophthalmia neonatorum in the newborn, bilateral keratoconjunctivitis in young cats associated with active rhinotracheitis, and unilateral or bilateral ulcerative keratoconjunctivitis without associated systemic disease in young and adult cats. I believe all cats may have feline herpes virus in their system. Stress in any form, ie, additional systemic disease, systemic or topical corticosteroids therapy, or emotional stress (new pet, new home) may cause a recrudescence of a latent infection.

There are three forms of ulcerative keratitis seen in the adult cat. All three forms may be unilateral or bilateral. The cat may be presented with severe blepharospasms, conjunctival hyperemia, or serous to seromucoid ocular discharge. When the cornea is closely examined, small linear punctate or branching ulcers termed dendritic ulcers may be found without associated corneal vascularization or edema. Unstained, these ulcers will have a ground glass appearance. Early cases may have only the pain and severe conjunctival involvement without corneal ulcers. Cases may also present with no subjective signs of pain, little to no conjunctival hyperemia yet multiple linear and punctate superficial ulcers and a history of increased tearing.

In a more chronic form of the disease, the ulcers may coalesce, forming larger superficial ulcers termed geographic ulcers. In this form, superficial blood vessels and mild corneal edema may be present.

In severe cases, the corneal stroma is involved. In this form, interstitial edema may be severe, preventing visualization of the anterior chamber. Corneal ulcers extend into the stromal layers and deep limbal vascularization is present. This form may involve not only herpes virus infection but also an immune reaction.

In all three forms of the disease, tear production may be decreased. Secondary anterior uveitis may be present especially with the stromal form of the disease.

Diagnostic tests are not readily available. Some tests are lengthy and expensive while other tests have a high incidence of false-negative results. The different tests include conjunctival smears for cytology and indirect fluorescent antibody tests, virus isolation, and serologic tests for serum neutralizing antibodies and for hemagglutination inhibition for antibodies. A polymerase chain reaction (PCR) technique has proven to be the most reliable. It is more sensitive and has fewer false-negative results than the IFA test. Its drawbacks include the fact that few laboratories do the procedure and false negatives are still possible.

Sequelae to feline herpes virus include eosinophilic keratitis, corneal sequestrum, symblepharon, keratoconjunctivitis sicca (KCS), conjunctival cysts, and scarring of the nasolacrimal puncta and duct.

Response to therapy and clinical signs may be the best diagnostic test. If the condition worsens with topical corticosteroids, a herpes infection is frequently indicated. With specific antiviral drugs, response to therapy is usually rapid. Within 48 hours, hyperemia and blepharospasms will reduce.

Three topical medications are now available with specific antiviral activity: adenosine arabinoside (Vira A®, Parke-Davis, often unavailable), trifluridine (Viroptic®, Monarch Pharmacy), trifluridine generic and idoxuridine solution and ointment generic. Generic drugs are available from many formulating pharmacies such as Wedgewood Pharmacy (1-800-331-8271) and Veterinary Pharmaceuticals (1-800-682-4664). Trifluridine has been found to be the most effective in feline herpes virus. Initially, one drop is used every two hours for the first 24 hours and then every four to six hours. Additional therapy may include tear replacements, topical antibiotics and atropine if the anterior uveitis is significant.

Unfortunately, all antiviral drugs can cause local irritation manifested by increased blepharospasms and hyperemia of the conjunctiva and lid margins. Due to the frequent incidence of adverse reactions to other drugs, ie, atropine and antibiotics, minimal drugs should be used. In cases of severe drug reactions, the topical antiviral must be changed.

Epithelialization should be complete within seven days. Topical corticosteroids can then be added to the treatment regime if corneal edema or vascularization is present and severe. The antiviral drug should be continued for at least two weeks following remission of all clinical signs.

Recurrence rate is high and the client should be so advised. Cases of recurrent attacks, or severe stromal involvement should be evaluated for feline leukemia virus (FeLV) and feline immunodeficiency virus (FIV). In some cases, antiviral medication is continued throughout life at once daily or every second day to prevent recurrence.

L-lysine is viral-static as the amino acid lysine replaces arginine in the replicating virus. The amino acid L-lysine has been used at a dose of 500 mg b.i.d. This is readily available at pharmacies and health food stores. The primary efficacy of this drug in herpes is suppressing recurrence. The side effects are rare (gastritis). The various products available are listed in Table 1 and Figure 1 along with the cost to the veterinarian as of 2/07.

Interferon (Roferon-A®, Roche Laboratories) has also been used in several cases that are refractory to routine therapy or show a high incidence of recurrence. In theory, it should be inhibitory to virus growth. The stock product of Roferon A is diluted to 30 IU/mL and dosed at 1 mL orally once or twice daily. The efficacy again is difficult to prove but clinically I feel it has helped to control difficult cases. Some ophthalmologists have reported good results using a topical interferon alpha 2b available from formulating pharmacies.

Purine nucleoside analogues have been used in humans for their inhibitory activity against several human herpes viruses. Several investigators have questioned their efficacy in feline herpes. Neutropenia and renal disease have been reported as adverse side effects with these drugs. Most recently, famciclovir (Famvir®) has been used in cats with good clinical results without adverse side effect. The recommended dosage has varied tremendously from ¼ of a 125-mg tablet b.i.d. to a 125-mg t.i.d.! In a study by Thomasy et al, famciclovir was given at a dosage of 90 mg/kg t.i.d. for 21 days. No physical, hematologic, or biochemical changes were noted.

It is important to educate the client that the FHV-1 is seldom totally eliminated from the affected cat. The virus becomes quiescent only to relapse under stress. The aim of long-term therapy is to reduce exacerbations.

Table 1. Cost Comparison of L-Lysine Products (as of 3/06)

Product	No. of 500-mg Doses per Unit	Units Needed for 365 Days / 730 Doses	Cost / Unit	Cost / Year
Viralys Powder 100 grams, Vet Solutions	155 (2 scoops)	5 jars	$7.49	$37.45
Over The Counter Various sizes, TMTC	Varies	Varies	Varies	$40.66 ($14.88–79.92)
Viralys Gel 5 ounces, Vet Solutions	60 (½ teaspoon)	13 tubes	$6.38	$82.94
L-Lysine Solution 100 mL, Wedgewood	50 (2 mL)	15 bottles	$21.21	$318.15
Enisly-F 15 mL, Vetoquinol	7.5 (2 mL)	98 tubes	$3.13	$306.74
Duralactin Feline L-Lysine 32.5 mL, VPL	6.5 (5 mL)	113 syringes	$6.15	$694.95

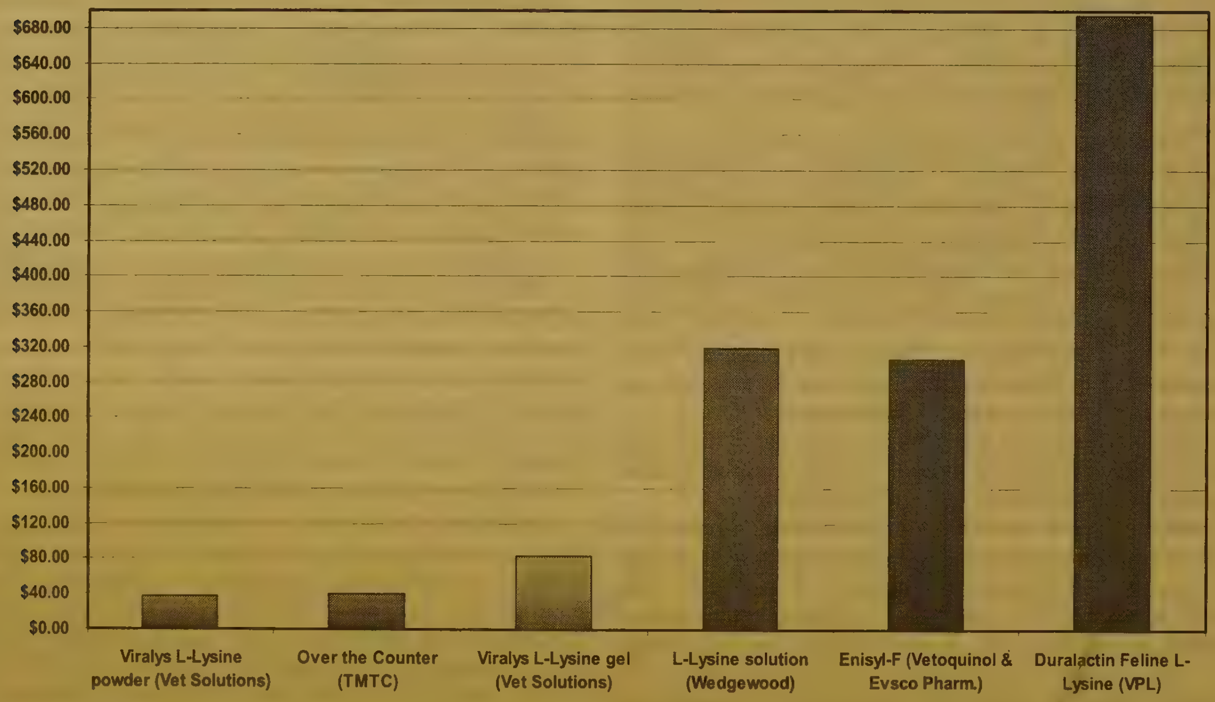

Figure 1. L-Lysine b.i.d : Annual Cost to Veterinarian of 500 mg as of 2/07.

GLAUCOMA

The incidence of glaucoma in cats is much lower than dogs and the clinical signs are not as obvious. Buphthalmia is present in chronic cases but extremely buphthalmic globes may still be visual. Cats also develop much less corneal edema and episcleral injection than dogs even with intraocular pressure (IOP) as high as 60 mmHg.

Primary glaucoma is usually bilateral and has been reported in Siamese, Persian and domestic shorthair cats. These individuals are usually presented with buphthalmia, subluxated lens and decrease vision. Congenital open and closed angle glaucoma is also seen as a bilateral disease with multiple ocular defects, primarily in the DSH.

Feline aqueous humor misdirection syndrome (FAHMS) is a unique form of glaucoma seen in cats at an average age of 11.7 years. The reported incidence is greater in females and in my practice, Persians are over represented. The affected globe has a dilated pupil with a sluggish PLR resulting in an anisicoria. The anterior chamber is extremely shallow. Frequently, an anterior capsule or cortical cataract is present. As in most cases of glaucoma in cats, corneal edema and episcleral injection are not present. Optic disc atrophy may be present but is difficult to detect in cats. A membrane develops posterior to the iris, preventing the normal flow of aqueous anteriorly resulting in the anterior displacement of the iris and lens. The inciting etiology is unknown.

A form of primary open angle glaucoma has been seen in young DSH. These cases have bilateral lens subluxation, deep anterior chambers, iridodonesis, anisicoria, and moderate elevations in IOP.

Secondary glaucoma is most frequently due to severe anterior uveitis. Diffuse iris melanomas in cats are a common cause of glaucoma. These cases may be presented with a dark brown iris, irregular pupil, pigment on the anterior lens capsule, and a buphthalmic globe.

Cats with primary glaucoma are treated similarly to dogs, but they have less tolerance to drugs. The carbonic anhydrase inhibitor (CAI) dichlorphenamide is used at a total dose of 12.5 to 25 mg s.i.d. to b.i.d. Side effects include acidosis, lethargy, loss of appetite and weakness. Potassium replacement is frequently indicated in cats. Two topical CAI, 2% dorzolamide (Trusopt®) and brinzolamide (Azopt®) have been used in cats t.i.d. Both drugs have been well tolerated with a good clinical response. Pilocarpine 1% and demecarium bromide (Wedgewood Pharmacy, 1-800-331-8272) are also used s.i.d. to b.i.d. but may cause local irritation and diarrhea. Miotics in no form should be used in FAHMS. It has been suggested that the beta-adrenergic blocker (Timoptic® 0.5%) is more effective in cats than dogs. Latanoprost (Xalatan®) and similar prostaglandins should not be used in cases of FAHMS or most secondary glaucoma. The prostaglandins may be beneficial in primary open-angle glaucoma.

Secondary glaucoma is treated similar to that in dogs; ie, treat as in anterior uveitis. Intraocular pressures should be monitored. As inflammation improves, the IOP should decrease. Identification of the primary cause of anterior uveitis (FeLV, FIP, *T. gondii*, *Bartonella*) must be attempted

CONJUNCTIVITIS

Unlike dogs, most cases of conjunctivitis in cats are infectious and are associated with specific diseases (Table 2). Noninfectious causes of conjunctivitis cannot be ignored (Table 3). Diagnosis is often based on history and clinical signs, both systemic and ophthalmic. Conjunctival cytology results are variable and unpredictable and depend on the stage of the disease. Serology and PCR techniques are available for most infectious etiologies. There is no test that is 100% accurate and remember, more than one microbe may be involved (polymicrobial infection).

Treatment should be directed at the specific pathogen. Keep in mind, many topical antibiotics (Terramycin®, erythromycin) and antivirals (trifluridine, IDU) may cause allergic reactions in cats. Although they may be effective for the microbe suspected, their allergic reactions may be worse than the disease itself.

I prefer to treat with minimal topical medications. I have used azithromycin (10 mg/kg q.d.) or doxycycline (10 mg/kg b.i.d.) for suspected cases of *Mycoplasma*, *Chlamydophila*, or *Bartonella*.

In suspected cases of FHV-1, it may be necessary to treat with both topical antiviral and oral viral-static L-lysine.

The etiology of eosinophilic conjunctivitis remains unknown. The severe hyperemia of the conjunctiva is characterized on cytology by eosinophils and mast cells. This would implicate a yet to be identified antigen and subsequent allergic reaction. The condition responds favorable to systemic corticosteroids and megestrol acetate. This would suggest a relationship to eosinophilic keratitis, believed to be initiated by an immune reaction to FHV-1.

Lipogranulomatous conjunctivitis is a poorly understood disease seen in middle to older aged cats. It may be unilateral or bilateral. Opaque white nodules are found in the conjunctiva, primarily in the palpebral surfaces and fornices. A generalized hyperemia of the conjunctiva is also present. The source of the lipid and the initiating cause of this disease have not been identified. To date, therapy has had limited success. Oral antibiotics (doxycycline) as well as topical corticosteroids and antibiotics have been used to reduce the inflammation. Solitary nodules are surgically excised, or removed, by laser or cryosurgery. Several cases have been positive for *Bartonella* and may explain their response to doxycycline.

Table 2. Etiologies of Feline URI and Conjunctivitis

Feline Herpesvirus (FHV-1)	Feline Calicivirus (FCV)
Bartonella henselae	*Bordetella bronchiseptica*
Chlamydophila feli (C.psittaci)	*Cryptococcus neoformans*
Mycoplasma felis	

Table 3. Secondary Conjunctivitis in Cats

- Adnexal Disease
- Corneal Disease
- Retrobulbar mass
- Dacryocystitis
- Anterior Uveitis
- KCS
- Allergic
- Trauma
- Neoplastic
- Parasitic

ANTERIOR UVEITIS

Anterior uveitis or iridocyclitis is inflammation of the iris and ciliary body. This will result in changes in the cornea, conjunctiva, sclera, or lens. Inflammation or infection of the posterior segment, ie, retina and optic nerve, may result in or be associated with an anterior uveitis. Many endogenous or infections diseases may result in an anterior uveitis (Table 4). Other etiologies include trauma to the globe, cornea, or lens.

Diagnosis of the etiology for many cases of anterior uveitis is difficult. Serology is often not diagnostic but can be submitted for most endogenous diseases. The age of the cat and associated clinical sings should also be considered.

Treatment is both topical and systemic. Topical treatment would consist of prednisolone acetate, nonsteroidal anti-inflammatory drugs (NSAIDs), and atropine in most cases. Systemic therapy would be dependent on the etiology of the anterior uveitis.

Table 4. Etiology of Feline Anterior Uveitis – Endogenous / Infectious

- Bacteria:
  - *Bartonella* sp.
  - *Mycobacterium*
- Viruses:
  - Feline Leukemia Virus (FeLV)
  - Feline Infectious Peritonitis Virus (FIPV)
  - Feline Herpes Virus (FHV-1)
  - Feline Immunodeficiency Virus (FIV)
- Mycotic:
  - All systemic mycotic infections
- Parasitic:
  - *Toxoplasma gondii*
  - *Cuterebra* larva
  - *Dirofilaria immitis*
  - *Metastrongylidae*
- Neoplasia:
  - Feline lymphosarcoma complex (LSA)
  - Metastatic neoplasia from a variety of primary sites
  - Primary intraocular neoplasia

THE CORNEA OF OLDER DOGS

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Geriatric care has become a very important aspect of veterinary medicine. Although older dogs can have many of the same corneal diseases found in younger dogs, there are three diseases unique to the geriatric dog.

INDOLENT ULCER

Although first described in the boxer, this disease can be found in any middle aged or geriatric dog; it is seldom seen in a young dog. The Golden retriever, West Highland white terrier, and Corgi breeds are commonly affected. The disease has also been referred to as a basement membrane dystrophy, boxer ulcer, refractory ulcer, superficial corneal erosion, canine dendritic ulcer, canine persistent superficial corneal ulcer, and recurrent erosions. The most recent name given this disease is spontaneous chronic corneal epithelial defect (SCCED).

There are two theories as to etiology. The most widely accepted etiology is a dystrophy involving the basement membrane of the corneal epithelium that results in nonadherence of the epithelium to the stroma. The second theory is a degeneration of the superficial stroma resulting in a thin acellular zone of hyalin collagen. The basement membrane and epithelium cannot adhere to this abnormal stroma. A diagnosis of indolent ulcer should not be made in the case of a recurring ulcer caused by KCS, ectopic cilia, exposure keratitis, or entropion.

The disease may be unilateral or bilateral. Uncomplicated cases are presented with only a mild squint, a mild increased lacrimation, cloudy area on the cornea, and mild conjunctival injection. The severe pain associated with most superficial ulcers is not present. When the cornea is stained with fluorescein, a border of light green will be seen around a dark green central area. This is caused by the dye undermining the loose redundant border of epithelium. After application of a topical anesthetic this redundant border can be easily stripped off with corneal forceps. Also, unlike other ulcers, there is no tendency for indolent ulcers to penetrate. They may remain superficial initially, elicit no vascular response, and persist for months.

Complicated indolent ulcers usually result from inadequate treatment. These show increased blepharospasms, corneal vascularization, and edema but still have only a superficial ulcer with redundant border.

Diffuse and severe corneal edema may be present at any stage of the indolent ulcer. This may represent a concomitant endothelial dystrophy. This increased edema may complicate the treatment and response to therapy.

Client education about this disease is important. The owner must realize this is a difficult disease to bring under control and recurrence rate is high; however, it will not lead to blindness. All cases will improve.

Initial treatment includes stripping off the loose border with forceps and a dry cotton swab. The new edge of the ulcer is then cauterized with 7% iodine and rinsed with a collyium. All of this can usually be accomplished with topical anesthetic with or without tranquilization. If the patient presents on topical antibiotics and is cooperative, a grid keratotomy may be performed instead of cautery. The cornea should be thoroughly irrigated prior to performing a grid keratotomy.

If there is indication of anterior uveitis, decreased intraocular pressure (IOP), or miosis, 1% atropine BID is dispensed and the animal is started on aspirin or other nonsteroidal anti-inflammatory drug (NSAID). Due to the corneal edema, NaCL ointment (Sodium Chloride, Akorn; Muro-128®, Alcon Labs; SoChlor®, Ocusoft) is started QID. Since this is not a bacterial infection and since they never penetrate, topical antibiotics are only indicated prophylactically if a grid keratotomy is planned. An Elizabethan collar or bucket is placed on the dog to discourage rubbing at the eye. This is an underrated and crucial step towards healing.

The eye is reevaluated in 3 to 5 days. If the cornea is reepithelized, and pannus is present, topical corticosteroids (dexamethasone/antibiotic combination) QID is added to the treatment regime. If the stain retention has reduced and the eye is comfortable, treatment is continued and the eye rechecked in 3 to 5 days. If there is no improvement or if the eye is painful, the previous procedure is repeated. If there is little response to the first two treatments, a more aggressive treatment is indicated. Under general anesthesia the epithelium is again removed using a cotton swab, corneal forceps, or by gently scraping with a No. 64 Beaver blade. All loose epithelium is removed; using a 22- to 25-gauge needle a grid keratotomy is performed. The entire ulcer area is scored to approximately 1/3 the thickness of the cornea. The grid lines are approximately 3 to 4 mm apart and extend 2 to 3 mm into the intact epithelium. Following this procedure, a temporary tarsorrhaphy is used to protect the cornea and make the eye more comfortable. The tarsorrhaphy is left in place for 7 to 10 days. The success rate of this procedure has been excellent. Also, the recurrence rate following this procedure is much less than cases that initially epithelialized without surgery. The reepithelialization and low recurrence is due to the fine scars that form from the deep stroma along the keratotomy line to the epithelium.

Other treatment regimes used by veterinary ophthalmologists include therapeutic soft contact lenses, cyanoacrylate adhesives, epithelial growth factors, and polysulfated glycosaminoglycan (Adequan®). Topical and or oral tetracycline have also been used to improve the ability of the epithelium to adhere to the underlining stroma. In my opinion, conjunctival flaps and stromal keratectomies are never indicated.

There are no proven effective means of preventing recurrence. Continual BID treatment with NaCL has reduced the incidence of recurrence. The use of estrogen, testosterone and thyroid replacements have not been found to be effective in preventing recurrence.

ENDOTHELIAL DYSTROPHY

This disease is most commonly found in the Boston terrier, Chihuahua, and dachshund, but is also seen in the Basset hound, English springer spaniel, West Highland terrier, wire-haired fox terrier, cocker spaniel, and even mixed breed dogs.

The endothelial layer of the cornea degenerates allowing water from the aqueous to enter the stroma resulting in corneal edema. This blue cloudy discoloration is frequently misinterpreted as a cataract by owners and glaucoma by veterinarians. This is especially true in cases that have progressed to visual impairment. As the disease progresses, the epithelium becomes involved with elevated clefts of water termed *bullae*, hence the term *bullous keratitis*. In severe cases the cornea can become so thickened, especially axially, that it becomes cone shaped and may even protrude through the closed lids. The term *keratoconus* is used to describe this condition.

The disease is usually bilateral in the common breeds, but may present as a unilateral disease first appearing in the temporal cornea. Initially, the condition is nonpainful, but as bullae are formed and rupture resulting in corneal ulcers, the condition becomes painful. Deep stromal ulcers and descemetoceles may form due to the protease enzymes released or secondary bacterial infections. Anterior uveitis may also contribute to the pain. In chronic cases, neovascularization of the cornea is often present.

Diagnosis is based on clinical findings, history, and breed. Other causes of endothelial damage and corneal edema such as anterior uveitis and glaucoma should be evaluated.

Treatment is palliative at best. Early cases with non-vascularized corneas are controlled with topical hypertonic sodium chloride ointments two to six times daily. If neovascularization is present, topical corticosteroids are used to control the vascularization. If corneal ulceration is present, topical antibiotics are used in addition to the sodium chloride.

Deep stromal ulcers may require a nictitans flap or temporary tarsorrhaphy. Descemetoceles may require a conjunctival flap or corneal graft. These procedures are not curative for the disease but are used only to maintain the globe and vision following a complication.

It is important to control anterior uveitis if present since it adds to the endothelial damage and resulting edema. Anterior uveitis is seldom present without corneal ulceration, so corticosteroids are only given systemically. Systemic antiprostaglandins and topical atropine may also be indicated.

Once brought under control, cases are maintained with topical sodium chloride two to four times daily and topical corticosteroids daily or an alternate days if corneal vascularization was present. Cases are rechecked every 6 months and owners are advised to watch closely for progression, involvement in the other eye, if initially unilateral, and subjective signs of pain.

CALCIUM DEGENERATION

This is a poorly defined disease seen in older dogs, also known as band keratopathy. Initially, lesions are restricted to the axial cornea and consist of an irregular circular lace-like white opacity. The white area is superficial but does not elevate above the cornea and has a "grainy" appearance densest axial. Initially, the deposits cause little corneal reaction, ie, edema or neovascularization or pain. Lesions are usually bilateral, but not symmetrical.

As the disease progresses the white plaques get denser and the central area becomes edematous and may ulcerate. Superficial vessels extend to the lesion. In this advanced stage, the dog may develop an associated anterior uveitis and may manifest signs of ocular pain.

Diagnosis is based on clinical signs and may be confirmed by a biopsy. Treatment is dependent on the stage of the disease. In advance cases with ulceration and anterior uveitis, topical antibiotics, atropine and antiprostaglandins (Ocufen®, Allergan Labs; Voltaren ®, Ciba Vision) are used in addition to a product to chelate calcium. The chelating drug could be 1 mL dipotassium ethylenediamine tetracetate (Sequester-Sol®, Cambridge Chemical Products) added to 15 mL of a tear replacement or edetate disodium ophthalmic gel 1%, available from Wedgewood Pharmacy. Either product is used every 2 to 4 hours initially. The efficacy of the treatment is difficult to evaluate. Clinically, it appears to control the progression of the disease, allows the cornea to re-epithelialize, and subjectively reduces the calcium deposits. Once epithelialization is complete, topical corticosteroids are used to reduce the vascularization.

The chelating drug is used TID to control the disease after the initial treatment. Its use has significantly reduced the recurrence of ulcers and pain but does not clear the cornea completely.

The initial cause of the deposition of calcium is unknown. It has been suggested that Cushing's disease or hyperadrenocorticism is associated with the syndrome. This should be considered and evaluated in all cases. In cases with calcium degeneration and Cushing's disease the treatment of the latter does not cure the corneal degeneration.

TREATING GLAUCOMA—NOT FOR THE FAINT-HEARTED

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The popularity of cocker spaniels and the high incidence of ocular disease in the breed make cockers a very important part of an ophthalmology practice. Primary inherited glaucoma is the most devastating ocular disease seen in this breed. This breed is also a perfect "case study" for glaucoma in all breeds. Two crucial determinations must be made in dealing with glaucoma. This disease must first be differentiated from other ocular diseases (some inherited) with similar clinical signs. Secondly, primary glaucoma must be differentiated from secondary glaucoma. Without these two determinations, effective therapy is impossible and a reasonable prognosis cannot be established.

This article emphasizes the correct diagnosis of glaucoma and the differentiation of primary vs. secondary glaucoma. The diseases most frequently misdiagnosed as glaucoma and the reasons for this error will be discussed. Several diseases, such as episcleritis, endothelial dystrophy, facial paralysis, phacolytic uveitis, keratoconjunctivitis sicca, and progressive retinal atrophy, also have a breed predisposition in cockers. Other diseases, such as anterior uveitis with multiple etiologies, serous retinal detachment, optic neuritis, chorioretinitis, sudden acquired retinal degeneration, and retrobulbar masses, when they occur in the cocker spaniel, are often misdiagnosed as glaucoma.

GLAUCOMA - DIAGNOSIS

A diagnosis of glaucoma cannot be made based solely on clinical signs. This is because in the early stages of primary glaucoma, the signs and intraocular pressure may fluctuate. It is quite possible to measure the intraocular pressure (IOP) and find that it is within the normal range. However, before a definitive diagnosis of glaucoma can be made, an elevated IOP must be demonstrated.

Tonometry is the technique of determining intraocular pressure. Normal IOP in the dog is 10 mmHg to 25 mmHg. The normal range will also vary with instrumentation. There should be a difference of no more than 8 mmHg between the two eyes. A diurnal variation in IOP in the dog results in higher IOP in the morning. Glaucomatous eyes show a greater daily variance.

Applanation tonometry is economically feasible for the general practitioner. The Tono-pen X-L (Dan Scott, 1-888-TONOPEN, Columbus, OH) is a miniaturized tonometer slightly larger than a fountain pen. It yields an accurate digital readout of IOP. It is expensive, but is the instrument of choice if you are going to screen animals for glaucoma or monitor the response to therapy. IOP in normal dogs ranges from 10 to 15 mmHg.

Even if the only technique available is digital, the IOP must be determined to make the diagnosis of glaucoma. To say that an eye "looks" hard and then treat for glaucoma will lead to frequent misdiagnoses.

Ophthalmoscopy, either direct or indirect, is important as a diagnostic procedure, but possibly even more important in determining the prognosis for vision after the IOP is controlled. If by examination, it is determined that an eye is irreversibly blind, the choice of therapy is significantly different from that of a potentially visual eye. This difference will be discussed under treatment. Gonioscopy is performed by ophthalmologists to diagnose and confirm primary glaucoma.

MISDIAGNOSIS

The misdiagnosis of glaucoma is most frequently caused by the failure to measure the intraocular pressure of the case presented. The diagnosis is based erroneously on one or more of the "cardinal signs" of glaucoma. The following is a brief discussion of the diseases that have frequently been misdiagnosed as glaucoma.

Episcleritis/scleritis is common in the cocker spaniel as a unilateral or bilateral disease that is believed to be immune mediated. It may present as a nodular or diffuse scleral swelling. Secondary vascularization and edema of the cornea is common. Posterior scleral involvement may result in optic neuritis and retinal detachments. Involvement of the uvea may lead to anterior uveitis. Treatment consists of topical corticosteroids, cyclosporine and/or tacrolimus, in some cases, oral corticosteroids and azathioprine. Cases are controlled but never cured.

Endothelial dystrophy is normally a bilateral disease in older cocker spaniels. The diffuse corneal edema may be associated with superficial vessels, epithelial bullae, and superficial and deep ulcerations. Treatment consists of topical hyperosmotics in the form of sodium chloride ointment. In many cases, topical corticosteroids are needed to control corneal vascularization. Control of the disease is usually possible.

Facial paralysis in the cocker is most often associated with chronic otitis media. In addition to the lack of a blink response and the wide palpebral fissure resulting in the increase "scleral show", the lip and ear on the affected side may droop or sag. Drooling from the affected side of the mouth is common. Associated keratoconjunctivitis caused by exposure or decreased tear production is common. Treatment is aimed at correcting the primary cause and protecting the globe with tear replacements, antibiotic and anti-inflammatory drugs. Once the disease progresses to the "contracture phase" with reduced palpebral fissure, pulled lip, and deviated nose, the condition is irreversible.

Progressive retinal atrophy in the cocker spaniel is normally a slowly progressive disease. However, in some cases, the owners are unaware of the disease until late in the course when the dog's pupils become dilated and unresponsive. When presented at this stage, they may be misdiagnosed as glaucoma.

Sudden acquired retinal degeneration (SARD) presents as an acute blindness. The dilated and often sluggish pupils and associated conjunctivitis lead to the diagnosis of glaucoma. The correct diagnosis is presumed based on history and ophthalmoscopic examination showing tapetal hyperreflectivity and sacculation of vessels. The diagnosis is confirmed by electroretinography.

Anterior uveitis in the cocker may be caused by many of the infectious, neoplastic, and immune mediated diseases reported in the dog. Young cockers, often less than a year of age, can be presented with an acute onset of unilateral or bilateral lens induced or phacolytic uveitis. This is caused by the rapid maturation of the cataract and liquefaction of lens protein, followed by leakage of protein through the lens capsule. All cases of anterior uveitis have the potential to become secondary glaucoma. Intraocular pressure should be closely monitored. Treatment first consists of identifying the primary etiology when possible. Topical mydriatics and cycloplegics, i.e. atropine, are usually indicated. Based on severity and etiology, topical and/or systemic corticosteroids and nonsteroidal anti-inflammatory drugs (NSAIDs) are also indicated.

Acute blindness due to posterior segment disease, may be seen in the cocker spaniel as in any breed. Chorioretinitis from a multitude of etiologies including infectious, neoplastic, metabolic, and toxic have been seen in cocker spaniels. Optic neuritis due to cryptococcosis, scleritis, and presumed immune mediated disease has been reported. All of these cases have been misdiagnosed as glaucoma due to the acute blindness, dilated pupils, associated conjunctivitis, and the simple fact that they occur in the cocker. Treatment is dependent on the etiology and associated ocular and systemic diseases.

Keratoconjunctivitis sicca (KCS) in the cocker spaniel is a common and primary disease. Cases may also be caused by any and all of the reported etiologies of KCS. Advanced cases are misdiagnosed as glaucoma due to the corneal and conjunctival involvement and decreased vision. The backbone of treatment consists of cyclosporine or tacrolimus, tear replacements, and antibiotics with or without corticosteroids.

Retrobulbar tumors, myositis, and abscesses can be presented in any breed. The associated exophthalmia, ocular pain, and hyperemia often lead to the incorrect diagnosis of glaucoma. Treatment and prognosis is dependent on identifying the etiology through fundic examination, ocular ultrasound, and radiographs.

PRIMARY GLAUCOMA

Primary glaucoma, a rise in intraocular pressure without any “obvious” prior ocular disease, is common in the cocker spaniel. Cockers have a presumed inherited defect resulting in an abnormal development of pectinate ligaments. This condition, called goniodysgenesis, can range from a thickened ligament to a band of tissue, which blocks the drainage angle. Once “clinical” glaucoma is present, evaluation of the angle in the affected eye is difficult and often not diagnostic. Histologic examination is always indicted in the “first” eye with glaucoma. Goniodysgenesis in the enucleated eye tells you that the remaining “normal” eye is predisposed to a rise in IOP. Examination of the fellow eye by gonioscopy is indicated and usually diagnostic. A direct correlation between gonioscopy findings and IOP is not always present.

SECONDARY GLAUCOMA

Secondary glaucoma is a rise in IOP following other ocular diseases that interfere with the normal outflow pathway of aqueous. The most common causes of secondary glaucoma in the cocker include anterior uveitis due to multiple etiologies (phacolytic and sclerouveitis), and anterior lens luxations. Initially, the IOP may be low to normal due to decrease production of aqueous by the inflamed ciliary processes. As the inflammation is successfully treated, the ciliary processes again produce more aqueous. If the outflow pathway is blocked by a broad peripheral anterior synechia, a complete posterior synechia, or anterior lens luxation, the IOP will start to rise above normal. For this reason, it is mandatory to monitor the pressure during the treatment of anterior uveitis.

The differentiation of primary from secondary glaucoma is aided by the knowledge of the causes of secondary glaucoma and close examination of the fellow eye, which may include gonioscopy of the drainage angle, detection of a mild aqueous flare, or lens subluxation.

TREATMENT– EMERGENCY GLAUCOMA

Acute congestive glaucoma is frequently presented as an emergency. These individuals are presented with all of the cardinal signs of glaucoma, (steamy cornea, episcleral injection, dilated pupils and blindness) plus IOP greater than 60 mmHg. Seldom does the IOP rise rapidly from normal. These cases are usually the result of chronic primary glaucoma or secondary glaucoma due to anterior uveitis or anterior lens luxation. They are true emergencies because, regardless of cause, if the IOP remains elevated in the range of 60 mmHg for greater than 24 hours, the prognosis for vision is very poor. It is important to differentiate primary from secondary glaucoma, since the etiology significantly affects the treatment.

In all cases of acute glaucoma, subcutaneous (SC) or oral carprofen (Rimadyl®, Pfizer Animal Health) will reduce the signs of pain. Its most significant effect is seen in secondary glaucoma.

Systemic corticosteroids are indicated in secondary glaucoma. Their efficacy in primary glaucoma is questionable, but can do no harm. I prefer intramuscular (IM) prednisolone, but intravenous (IV) dexamethasone phosphate is also very effective.

Systemic hyperosmotics are one means of rapidly lowering IOP in cases of acute glaucoma. Oral glycerin (2.2 mL/kg) or IV 20% mannitol (11 mL/kg) is given. In secondary glaucoma, the value of these drugs may be reduced. This is especially true in cases of active inflammation since the blood vitreous barrier is not intact. In these cases, mannitol, due to its greater molecular weight, may be the hyperosmotic of choice. Hyperosmotics are beneficial in cases of anterior lens luxation. The hyperosmotics should not be repeated more than twice during a 48-hour period. Water must be withheld for two to four hours. Glycerin may cause emesis and a transient diarrhea. Hyperosmotics frequently lower the IOP in primary glaucoma in 30 to 40 minutes. Furosemide has no effect on IOP.

The choice of miotic versus mydriatic is not always clear-cut and is very critical. If severe corneal edema prevents visualization of the pupil or if you cannot decide between primary and secondary glaucoma, their use should be delayed until the previous treatment response is evaluated.

In cases of known primary glaucoma, 1% pilocarpine is given every 15 minutes for one hour and then every 2 to 4 hours for the next 48 hours. The miotic effect of pilocarpine is not instantaneous. Ocular irritation, hypersalivation, and diarrhea are possible side effects.

Latanoprost (Xalatan®, Pharmacia and Upjohn) and Travoprost (Travatan®, Alcon) are new products that are being used by ophthalmologists. They are prostaglandin F analogues, and increase uveoscleral outflow. These drugs have been used to quickly lower the IOP in primary glaucoma. One drop has lowered IOP from a 60 mmHg to less than 20 mmHg in a half an hour! Severe miosis is associated with the hypotensive affect and could complicate a secondary glaucoma due to anterior uveitis or anterior lens luxation.

In cases of known secondary glaucoma due to miosis with posterior synechia or primary anterior lens luxation, mydriatics are indicated. Atropine 1% every 15 minutes for one hour then every 12 to 24 hours is the drug of choice. Systemic atropinization is possible. In addition to the cardiac effect and decrease salivation, decrease tear production is possible. The STT should be evaluated prior and during treatment.

Systemic corticosteroids are continued in secondary glaucoma if not contraindicated. Topical prednisolone or dexamethasone products are started every 4 to 6 hours.

Antiprostaglandin therapy is continued in secondary glaucoma using aspirin 20 mg/kg b.i.d., carprofen, or any of the other NSAIDs. Topical .03% flurbiprofen sodium (Ocufen®, Allergen) or diclofenac (Voltaren®, Ciba Vision) is instituted in severe cases every 4 to 6 hours.

After the initial therapy, treatment will continue for the next 48 hours based on etiology of the glaucoma. Carbonic anhydrase inhibitors are given orally in primary glaucoma. Their use in secondary glaucoma is greatly reduced since they only act on the active production of aqueous, which is already reduced in cases of active inflammation. If the IOP starts to rise as the inflammation improves, CAI may be indicated.

Surgery is seldom indicated on an emergency basis. Paracentesis of aqueous is never indicated.

MEDICAL TREATMENT OF PRIMARY GLAUCOMA

Carbonic anhydrase inhibitors (CAI) are used to reduce the active production of aqueous by no more than 50%. Therefore, they reduce total production by only 25%. Maximal effect is seen 4 to 8 hours after administration. Dichlorphenamide and methazolamide are chosen primarily due to decreased incidence of side effects. The side effects of CAI include polyuria and polydipsia and gastric irritation and emesis. Acidosis manifested by rapid breathing, emesis, diarrhea, and salivation; uneasiness is also possible. This, if it occurs, is usually transient and requires no specific treatment, but the dosage of the CAI should be reduced. Hypokalemia is also possible and this is manifested primarily by muscular weakness and mental confusion. This can be treated by salting the animal's food with a potassium salt, feeding bananas, or giving a potassium replacement such as potassium gluconate (Koan® Elixir, Adrea, 20 mEq/15 mL or Tumil-K® tab., 2 mEq, Daniels). This hypokalemia is not life threatening but the CAI dosage may have to be reduced. Urticaria has also been reported in dogs.

Two topical CAIs, 2% dorzolamide hydrochloride (Trusopt®, Merck) and 1% brinzolamide (Azopt®, Alcon), are now available. Topical administration should eliminate the side effect of gastric irritation. Whether the hypotensive effect is due to direct action at the nonpigmented ciliary epithelium or through systemic adsorption is not clear. Both drugs are used t.i.d. A severe blepharitis has been seen rarely with the use of these drugs.

Parasympathomimetics are used in the treatment of primary glaucoma because they increase the coefficient of outflow or the rate at which aqueous leaves the drainage angle. Their miotic effect is not directly correlated with their ability to increase aqueous outflow but can be used as a rough indicator. In the case of greatly elevated pressures, the miotic effect of these drugs is limited until the pressure is lowered with hyperosmotics. Pilocarpine l% or 2% is used initially every 4 to 6 hours. Higher concentrations show little to no additive hypotensive effect and can be very irritating. A 4% pilocarpine gel (Pilopine® HS Gel, Alcon) has been used at bedtime in place of the lower concentration solutions. The clients should be advised that in most cases initial irritation from topical pilocarpine will be manifested by chemosis, hyperemia, and blepharospasms. A severe miosis and aqueous flare may be detected. In the vast majority of cases, this is transient and the owners are requested to continue the medication for 72 hours before a decision is made to switch or discontinue the drug. Diarrhea, even hemorrhagic, and hypersalivation are also possible side effects that will have to be monitored and dealt with accordingly.

Demecarium bromide (Wedgewood Pharmacy, 1-800-331-8272) is a cholinesterase inhibitor with similar action to pilocarpine. Its primary use is in the control of IOP following initial treatment with pilocarpine. It is also used in treating the "normal" eye with gonioscopically-affected angles, as in many cocker spaniels. It has been used successfully in cases in which pilocarpine was not tolerated. Demecarium bromide is effective when used twice daily. The owners are instructed that the pupil should be miotic every time they treat. Although this is not an absolute, the pupil getting large between treatments may indicate a rise in IOP.

Sympathomimetics decrease aqueous production and increase aqueous outflow. They are synergistic with the parasympathomimetics and CAI and are especially used in combination with these drugs. Epinephrine and dipivefrin solutions are available. Personal preference is .l% dipivefrin HCL (Propine®, Allergan or Dipivefrin HCL Ophthalmic Solution USP, O.1%, Falcon). Dipivefrin is an epinephrine prodrug that penetrates the cornea 17 times as readily as epinephrine and is converted to epinephrine in the uvea. It has minimal mydriatic effect. Like pilocarpine, these normally cause transient irritation. Superficial neovascularization of the cornea can be a problem with long-term therapy and may result in discontinuation of the drug. These drugs are usually used twice daily. Due to their decreased use in human glaucoma therapy, these drugs may soon be discontinued.

Prostaglandin analogues (Latanoprost, Xalatan® Pharmacia, Upjohn, and Travoprost, Travatan®, Alcon) are also available for the treatment of glaucoma. Their main mechanism of action is to increase aqueous outflow by the uveoscleral pathway. Severe miosis is associated with their use and a post-application rise in IOP caused by pupillary block has been reported. These drugs are used once or twice daily and are extremely expensive. Using these drugs in cases of secondary glaucoma can have severe sequelae.

Drugs from different classes are frequently used together in the control of glaucoma. However, two drugs from the same class show little additive hypotensive effect. Ideally, the IOP should be less then 20 mmHg when reevaluated to be considered well controlled. I like to measure the IOP just prior to treatment assuming the IOP will be at its highest level. I personally do not use combination drugs such as P2EI. The beta-adrenergic blocking agents have limited efficacy in the dog, in my opinion.

MEDICAL TREATMENT OF SECONDARY GLAUCOMA

These cases are usually controlled as described under emergency treatment. Controlling the inflammation prevents a return of the transient rise in intraocular pressure. Broad peripheral synechia and narrowing of the drainage angle may be the result of anterior uveitis. In this case, if the inflammation is under control and the IOP rises, CAI may be of benefit. Topical pilocarpine and other miotic are contraindicated and will usually cause increase inflammation, which may indirectly reduce IOP, but will not help control the uveitis or prevent recurrence of glaucoma.

SURGICAL TREATMENT

Surgery is indicated in the visual eye that cannot be controlled with medication. Surgery is also indicated in the irreversibly blind eye regardless of its response to medical therapy. The choice of surgery depends on the cause of glaucoma, the potential for vision, general health of the animal, and the owners' personal preference.

Secondary glaucoma may require an iridectomy or lens extraction. Filtering procedures such as a cyclodialysis and iridencleisis have a poor success rate in the dog with primary glaucoma. Implants to aid in filtering of aqueous are being explored and show promise. Laser therapy, termed *transcleral cyclophotocoagulation*, has also been used to selectively destroy ciliary processes and decrease aqueous production. A new procedure, called endoscopic cyclophotocoagulation (ECP) is currently being used at limited facilities. This procedure is much more invasive and expensive but appears to have fewer complications than previous procedures.

Cyclocryosurgery also is used in the visual eye that is not controlled with medication. Selective destruction of the ciliary body reduces the production of aqueous.

The blind eye is operated on to reduce ocular pain and, hopefully, to discontinue or reduce treatment depending on the other eye. Enucleations, cyclocryosurgery, injections into the vitreous to destroy the ciliary processes or an intraocular prosthesis are the options available to the owner. Personal preference is an intraocular prosthesis if the owner wants a cosmetic globe. In addition to the consideration of comfort of the animal, all of these procedures are economically feasible when you consider the cost of drugs to control IOP in a middle-aged dog for the remainder of his life.

"DOG BITE SEPSIS" ATTACKS THE CORNEA

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Keratomalacia or melting of the cornea is a severe, usually acute ulcerative condition of the cornea, with an associated anterior uveitis and severe signs of ocular pain. The destruction of the corneal stroma, ie, collagen fibers and extracellular matrix, by protease and collagenase enzymes results in a gray gelatinous appearance to the cornea. The corneal surface becomes irregular and elevated, producing the melting appearance. Irritation to the axons of the trigeminal nerve initiates an axonal reflex and dilation of vessels of the iris and ciliary body and results in the anterior uveitis and aqueous flare.

Many of the bacterial organisms that are associated with keratomalacia also release leukotactic toxins. Chemical mediators, released by damaged cells also cause leukocyte migration. Both reactions may produce hypopyon.

Proteases and collagenases, released in normal corneal healing, are important in remolding of damaged cornea. Melting ulcers develop when these enzymes are produced in excess. Many tissues, including the cornea, contain naturally occurring inhibitors of protease, that is, α-2-macroglobulin and α-1-proteinase inhibitor. The source of the proteases and collagenases may be bacterial *(Pseudomonas* spp is most common), fungal, polymorphonuclear neutrophils, corneal epithelial cells, and fibroblasts.

The proteases may be divided into two groups: matrix metalloproteases (MMP2, MMP9) and serine proteases (neutrophil elastase). MMPs require calcium and zinc as a cofactor and stabilizing ion, respectively, to be active.

Cases of keratomalacia require aggressive therapy, which includes topical and sometimes oral antibiotics, anti-protease agents, and treatment for the associated anterior uveitis. Bacterial cultures, regardless of prior antibiotic therapy, are always submitted on presentation. Topical antibiotics are started q2h to q4h. The antibiotics should be effective against gram-negative rods. Tobramycin or fluoroquinolones (Ocuflox®, Allergan; Quixin™, Santen) are my drugs of choice. If topical treatment is difficult or if the case is severe, oral fluoroquinolones are also used (Zeniquin®, Pfizer). Anti-protease agents (Table 1) are instituted as well. My product of choice is serum. The serum is taken from a healthy dog not currently on corticosteroids. The importance of the lack of systemic corticosteroids is not clear. The serum should be refrigerated and replaced with fresh serum every 8 days. Fibronectin, found in serum, also reduce the pain associated with keratomalacia and has been referred to as the "feel good factor." It has also been suggested that whole blood is more effective but I have not used this. The serum should be applied q2h to q4h. Combining a second anti-protease such as tetracyclines orally or topically in addition to serum may be beneficial.

Duralactin® (distributed by VPL) is a purified milk protein that has been shown to inhibit neutrophil migration and therefore could reduce the release of proteases. This drug cannot have any adverse affects.

The associated anterior uveitis is treated with topical 1% atropine once or twice daily and an oral nonsteroidal anti-inflammatory drug (NSAID). My choice is carprofen (Rimadyl®, Pfizer) or tepoxalin (Zubrin®, Schering-Plough Animal Health).

This aggressive schedule is maintained for the first 72 hours. If culture results dictate, the antibiotic may be changed. If the keratomalacia leads to an impending corneal rupture, surgery (eg, conjunctival flap) may be indicated.

CAPNOCYTOPHAGA

An unusual etiology for keratomalacia has been identified in dogs that share a common history of long-term antibiotic and corticosteroid therapy for various diseases including KCS and phacolytic uveitis among others.

These individuals are presented with acute keratomalacia. The etiologic agent of "dog bite sepsis," *Capnocytophaga* sp, has been isolated from severe corneal ulcerations in dogs and cats. This thin, gram-negative rod has a characteristic and distinguishing long fusiform appearance. The organism is a facultative anaerobe and grows best on blood agar in a 5% to 10% CO_2 environment. Colonies on blood agar are non-hemolytic but often pit the agar. Growth on the plate may take 2 to 4 days to form a flat, spreading pattern with irregular edges. If a portion of the colony is removed with a spatula, it has a yellow coloration. All of these findings separate the organism from other gram-negative rods but biochemical tests can positively identify this bacterium. There are three species that are found in the oral cavity of humans and these are the leading cause of periodontal disease in teenagers. *C. canimorsus and C. cynodegmi* may be found as part of the oral flora of dogs and cats. These species are the etiologic agent of dog bite sepsis, a potentially life-threatening disease especially in the immunocompromised patient. Isolates to date have not been speciated. Therefore, we do not know if the organism originated from human or canine contaminant. The drugs of choice are penicillin V potassium, amoxicillin, clindamycin, erythromycin, ciprofloxacin, and imipenem.

These cases are treated topically the same as keratomalacia which is described above. Erythromycin is applied every 2 to 4 hours initially, along with fluoroquinolones. Clindamycin is given orally and the prior ocular disease must also be concurrently managed.

Table 1. Anti-protease drugs.

Compound	Inhibitory Activity	Inhibitory Mechanism
Serum α-2-macroglobulin α -1-proteinase inhibitor	MMPs and serine protease	Entrapment of protease
Tetracycline Terramycin® Roerig Lab. Terak® Akorn Doxycycline Oxytetracycline	MMPs	Chelating agent Ca and Zn
N-Acetyl-cyctein 5–10% Mucomyst® (Roberts Pharmaceutical) Mucosil® (Dey)	MMPs	Chelating agent Ca and Zn
EDTA ointment 1% (Wedgewood Pharmacy)	MMPs	Chelating agent Ca and Zn
Synthetic MMP Inhibitor Galardin™ (Ilomostat), Glycomed, Inc.	MMPs	Chelating agent Ca and Zn

TEAR STAINING & PIGMENT & HAIRS O'MY: TREATING MEDIAL CANTHUS SYNDROME IN DOGS

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Chronic tearing, corneal and conjunctival pigment, and conjunctivitis in dogs are often the result of breed-related conformational abnormalities. This syndrome has been given many names, usually reflecting the abnormalities which are present in each individual patient. The abnormalities may be grouped into two larger categories: 1) Those often seen in brachycephalic and shallow-orbit breeds (the majority of the cases); and 2) Those found in mesocephalic breeds. The shallow-orbit breed abnormalities may include an abnormally large palpebral fissure (congenital euryblepharon); trichiasis from the nasal fold in brachycephalic dogs, medial caruncle and eyelids; medial inferior entropion; lagophthalmos with exposure keratoconjunctivitis, decreased corneal sensation, pigmentary keratitis or conjunctivitis; and chronic tearing. Breeds with deeper-set eyes may have medial canthus eyelid furrows, and an ectropion and entropion combination or diamond shaped eyelid openings. Both groups may have the additional problems of distichia, ectopic cilia, imperforate puncta (uncommon), and secondary *Staphylococcus* sp. allergic conjunctivitis. Most of these abnormalities may be improved or controlled with surgery (blepharoplasty), resulting in the decrease of clinical symptoms, and improved comfort of the patient. Complete resolution of the clinical signs is uncommon; therefore, client education is important so that expectations for improvement are realistic.

A complete eye examination should be performed on all animals to rule out other causes of these symptoms. This exam should include flushing the nasolacrimal ducts to rule out blockage or abnormal ducts and puncta, corneal staining to check for ulceration, Schirmer tear tests to rule out dry eye, and intraocular pressure measurement to rule out uveitis and ocular hypertension. The syndrome is diagnosed when one or a combination of the abnormalities listed below is present. Some dogs will present with blepharospasm, intermittent or constant, depending on whether they have good corneal sensation, and whether the irritant is enough to induce squinting. Even when there is no squinting, the eyelid conformation and the trichiasis may be causing the clinical changes of epiphora and excess pigmentation and inflammation. Distichia usually will cause squinting when it is a clinical problem.

MEDIAL CANTHUS SYNDROME IN SHALLOW-ORBIT BREEDS

This syndrome includes abnormalities that are the result of inappropriate breeding of purebreds by breeders who are not active in showing these breeds for conformation – that is – "puppy mills" and "backyard" breeders. Breeds included are the brachycephalic breeds of Shih tzu, Pekingese, pug, Boston terrier, Lhasa apso, English bulldog, and the shallow-orbit dogs including Maltese terrier, toy and miniature poodle and bichon frise.

Large Palpebral Fissure – Congenital Euryblepharon +/- Lagophthalmos and Exposure Keratitis

This problem is usually seen in brachycephalic breeds that have shallow orbits and breed-related exophthalmia, eg, Pekingese, Shih tzu, etc.[1] Diagnosis is made by observing very prominent globes (even more than typical for the breed) and excess white (conjunctiva) showing around the limbus. During the examination, the eyelids may be carefully retracted, and if the palpebral fissure is too large, the globe may begin to protrude. These individuals are more prone to proptosis, and caution should be used while the dog is under anesthesia or sedation to prevent this. The dog may have tear staining and nasal fold dermatitis because the eyes are so prominent, that the tears are forced over the eyelid edge and down the face because the protruding globe is blocking the nasolacrimal duct punctum.[1] When combined with decreased corneal sensation and lagophthalmos, euryblepharon can lead to exposure keratitis, recurrent ulceration, and delayed corneal healing.[2] These dogs also have a tendency to sleep with their eyelids partially open. Surgical correction using reconstructive blepharoplasty will be discussed below. Medial or lateral blepharoplasty may be recommended, depending on other abnormalities which may also be present.

Trichiasis – Nasal Folds, Medial Caruncle and Conjunctiva, Eyelashes and Eyelids

Prominent or very large nasal folds may be positioned to rub on the cornea. This is more common in the brachycephalic dogs that have been inappropriately bred with extremely short noses.[3] Symptoms include epiphora from corneal irritation, nasal fold dermatitis from the constant tearing, conjunctival redness, and vessels and pigment on the cornea where the hairs are contacting the cornea.[1] Diagnosis can be made by observing the hair from the nasal folds to determine if it touches the cornea. Sometimes the irritation is positional, and the hair only rubs when the dog is looking off to one side. Nasal folds may also push the medial canthus up and in toward the eye, causing inferior medial entropion with additional irritation to the cornea and conjunctiva, and epiphora from punctum blockage.

Grooming the hair short can be curative in some dogs; however, a careful evaluation of the anatomy is warranted, since the short brush-like hairs may be more abrasive after clipping. Conservative treatment may also include petroleum jelly used on the hairs to keep them flat and lubricated. Brachycephalic breeds with enlarged nasal folds may require surgical correction if the folds are causing a secondary keratitis, or if the nasal fold is so deep, that the dermatitis is severe. Surgical removal of part or the entire fold may improve or cure these symptoms.[1-3] Medial reconstructive blepharoplasty may also be used when the fold is contacting the cornea and may correct the problem without nasal fold reduction. The advantage of medial blepharoplasty (canthoplasty) is that it may correct medial inferior entropion, medial trichiasis, euryblepharon and epiphora, in addition to the nasal fold trichiasis. The technique will be discussed below

Nasal fold reduction is accomplished by either removing the medial fold only in the partial reduction or the entire fold. After complete surgical site preparation under general anesthesia, the fold area to be removed is clamped with a curved or straight Kelly hemostat for hemostasis. After removing the clamp, the skin fold is excised with curved Mayo scissors. The wound is sutured with 4-0 silk on a cutting needle, using simple interrupted sutures placed 3 mm apart.[1] The suture ends should be positioned to not rub on the cornea, an Elizabethan collar is used to prevent self-mutilation, and sutures are removed in 10 to 12 days.

Trichiasis from the medial caruncle and conjunctiva is common in the affected breeds, and causes corneal irritation with secondary tearing.[1,2] The hairs also aid in redirecting the tears from the puncta, and wicking them down the face. Rarely (since they are usually long soft hairs) do they cause enough irritation to initiate medial corneal vessels and pigment to occur. These hairs can be removed by either en bloc resection of the caruncle and the follicles in the conjunctival, or by cryonecrosis surgery using liquid nitrogen.[3] The cryosurgery is performed with either a small spray or contact probe, freezing the haired area and 2 mm of normal tissue around the hair follicle. Two freeze-thaw cycles are usually sufficient and do not cause excessive necrosis. Swelling and depigmentation are transient post-operative complications. Cryosurgery should not be performed if blepharoplasty procedures are performed at the same time, as healing of the sutured areas might be delayed. En bloc removal should be used instead.

Trichiasis may occur from eyelashes and eyelid hair that curl and irritate the cornea. Diagnosis is made by careful observation of the hairs touching the cornea, and locating their origin. Treatment is usually cryosurgery, using the same procedure described for the medial caruncle. Sometimes, eversion of the eyelid using one of the procedures for entropion surgery is necessary to lift the eyelashes from the corneal surface. This should be done conservatively, so that over correction does not cause exposure keratitis.

Medial Inferior Entropion

Medial inferior eyelid entropion is common in dogs that are brachycephalic or those with shallow orbits. In this type of entropion, the nasolacrimal punctum is covered or obstructed by the rolled-in skin, slowing tear drainage from that punctum.[2] In some cases, the tears run down the face, instead of draining into the nasolacrimal system. Surgical correction may improve the situation. It rarely completely corrects it. The most common surgery is the medial canthal V-plasty.[2] A triangular piece of skin is excised from the lower medial eyelid and the defect closed with interrupted sutures. The depth of the triangle that is removed is the same width as the amount of eyelid margin that is rolled under.[1] This procedure may also be done using a circular punch to remove a round area of skin. The major error with surgical correction is for the incision to be placed too far from the eyelid margin. The incision should be only 2 to 3 mm from the margin or approximately 1 mm from the haired-nonhaired junction. Closure is with interrupted 5-0 or 6-0 silk sutures on a cutting needle. The long side of the triangle should be parallel to the eyelid margin, and the center of that line should be closed to the apex of the triangle which is perpendicular to the punctum, providing the maximum amount of eyelid eversion in the center of the incision. Medial canthoplasty (blepharoplasty) can be used instead of the entropion surgery to correct the entropion,[4] and will be discussed below.

Pigmentary Keratitis and Conjunctivitis

Breeds predisposed to pigmentary keratitis are the brachycephalic breeds.[1] Low-grade keratitis seems to be the cause of this pigment and vessel migration into tissues. Many conditions seem to initiate the problem, namely; irritation from adnexal hairs (eg, nasal trichiasis from facial folds, medial entropion), lagophthalmos and euryblepharon, distichiasis, and dry eye. Treatment is aimed at correcting the primary problem such as lubricant therapy for dry eye, or canthoplasty surgery for lagophthalmos and exposure.[4] With medial canthoplasty surgery, the medial eyelid fissure is partially and permanently closed, thereby allowing greater corneal protection, alleviating medial entropion and trichiasis and allowing more effective distribution of tears. The eyelid fissure(s) may also be closed laterally using a lateral canthoplasty procedure.[4] Additional palliative therapy may include topical cyclosporine, or beta-radiation to clear the corneal scarring.[1] Cryosurgery may also prove beneficial to remove hairs or decrease pigment.[3]

Techniques for Blepharoplasty

Medial Canthoplasty – The ***simple medial canthoplasty*** is performed by excising the medial eyelid margins at a depth of 2 to 3 mm, starting 1 to 2 mm medial of both the upper and lower eyelid puncta and connecting the incision at the medial canthus.[4] The nasolacrimal puncta are identified and cannulated with suture before this procedure is started. This incision removes an equal amount of eyelid margin from the upper and lower eyelids at the medial aspect of the palpebral fissure and spares the nasolacrimal puncta. The incision is closed with a two layer closure consisting of a conjunctival suture line using 4-0 to 6-0 absorbable continuous suture, and a skin closure of simple interrupted 4-0 nonabsorbable sutures. An additional vertical mattress suture can be added to relieve tension from the primary suture line.

A more complicated procedure to perform is the **Roberts-Jensen pocket technique medial canthoplasty.**[4,5] The advantage is that the new canthus closure is stronger because the layers of tissue overlap in the pocket. This technique is also useful to treat medial entropion, as well as euryblepharon, lagophthalmos, and exposure keratitis.[4] By closing the medial canthus, the eye can be protected from minor nasal fold trichiasis. Each dog has different anatomic abnormalities, so this procedure should be evaluated under anesthesia before it is performed, to determine if the closure will produce the desired effect. The nasal folds can be reduced at the same time if necessary. The function of the upper nasolacrimal punctum is lost with this procedure. Initially, the eyelid margins are removed as above. The skin is then elevated from the conjunctival layer by splitting the cut-edge margin with a blade. The pocket is extended using tenotomy scissors, 10 to 15 mm into the lid, going superior to the upper eyelid, and going ventral on the lower eyelid. A triangular flap of the upper conjunctiva is cut with tenotomy scissors and its leading edge sutured into the bottom edge of the lower eyelid pocket using 4-0 single nonabsorbable suture. The suture is tied on the skin surface. The medial canthus is then closed with a two-layer closure as above.

A **simple lateral reduction canthoplasty** can be performed in a similar manner to the medial canthoplasty, and is technically an easier procedure.[4] This surgery also reduces the palpebral fissure; however, it does not treat medial inferior entropion. Medial trichiasis can be treated at the same time by cryosurgery or by en bloc resection. The tension on this closure is greater than for the medial procedure, however, the author has used this technique for many cases of euryblepharon with good success. To perform this surgery, the upper and lower eyelid and lateral canthus margins are excised approximately 4mm along each eyelid. Only the eyelid margin is removed to a depth of 2 mm. A two-layer closure is used as in the medial canthoplasty. A vertical mattress suture is useful to take the tension from the suture line while healing. These sutures should be left in place for 14 days, to ensure complete healing before the tension is applied to the new lateral canthus.[1,4] Less than 4 mm of the eyelid length can be removed if the euryblepharon is less severe. More than 4 mm should be evaluated very carefully.

A **modified Fuchs lateral canthoplasty** can be used when more tension will be placed on the lateral canthus, either from a more protruding globe, or because more of the eyelid length needs to be closed.[4] This technique uses a pocket technique to provide a two tissue layer closure.

Tear Staining Syndrome

Tear staining results from a discoloration from the overflow of tears down the face instead of the tears going down the nasolacrimal duct. The previous sections have discussed several reasons that the tears might not drain properly including medial inferior entropion, protruding globes (breed-related exophthalmos), nasal folds pushing conjunctiva and eyelid skin over the puncta, wicking of the tears by trichiasis, and imperforate or hypoplastic puncta.[1] The cause of the color of the staining is still not completely understood; however, the list of causes includes lactoferrin-like pigments, porphyrins, catacholamines, bacteria, yeast, or other minerals. Some of the dogs with this problem don't seem to have any of the underlying anatomic abnormalities in the list. The disease is somewhat perplexing since some dogs with trichiasis, etc. don't have tear staining or epiphora. Diagnosis is by observing the problem and ruling out other causes of tearing. If an underlying cause is diagnosed, it should be corrected using the appropriate treatments and/or surgery. Although the tear staining is called a "cosmetic" problem, a moist dermatitis may by present on the skin when the tearing is constant, and should be treated so that ulceration of the skin is prevented. Wiping the area dry and putting a thin layer of petroleum jelly on the skin daily, will improve the cleaning and skin health. If allergic conjunctivitis is suspected (the dog has skin or ear allergic disease, or the problem is seasonal), then topical treatment with antibiotics (gentamycin or triple antibiotic) or an antibiotic-steroid combination eye drop (triple antibiotic with hydrocortisone or dexamethasone) might improve the tearing.[1,2] Oral antihistamines are also worth trying in allergic dogs.

Treatment to stop the staining from the tears (does not stop the tearing itself) consists of oral tetracycline 5 to 10 mg/kg/day.[1] The mechanism is thought to be chelation by tetracycline of the pigment in the tears. This treatment works as long as the drug is given. Other treatments listed (and of unknown efficacy because reports are anecdotal) include chlortetracycline; oxytetracycline 25 to 50 mg/day 2 weeks on and 2 weeks off; doxycycline and niacinamide; tylosin, give a pinch in food once a day until the staining is gone, then every other day for one month, then twice each week; metronidazole 100 to 200 mg orally, once/day for 10 days of each month; and topical naphazoline HCl 0.1%.

Distichia and Ectopic Cilia

Distichiasis is the most common form of eyelash disease. Cilia arise from tarsal gland openings on the eyelid margin. The upper or lower eyelids can be affected. These cases must be evaluated carefully, as only those causing clinical signs should be treated.[1-4] Often, cocker spaniels, toy poodles, golden retrievers and weimeraners have a few fine soft lashes which are not causing a problem. In other breeds, the aberrant eyelashes are usually bristle-like. The main signs are epiphora, conjunctival injection, and blepharospasm. Secondary corneal damage may result.

- Treatment
  - **Manual epilation** is effective if there are a few distichia. The effect is only temporary and may facilitate healing of a corneal ulcer until permanent lash removal can be scheduled. It is also an effective aid to diagnosis, to determine if the distichia are the cause of the epiphora and/or squinting. Epilation should be curative if they are causing the problem.[1]
  - **Electrolysis** - A low current must be used to avoid eyelid scarring. A fine needle is run along the hair to the root, and then the current is turned

on. You may have to repeat this procedure several times in young dogs. Affordable and effective units are difficult to obtain. Some veterinarians employ a cosmetologist to do the procedure while they monitor the anesthesia and do the follow-up examinations.[1,2]

- **Cryoepilation** - Liquid nitrogen or nitrous oxide are used to form an ice ball at site of follicle. Eyelid depigmentation occurs and regrowth of some of the hairs can occur. Repigmentation occurs at approximately 16 weeks and the cosmetic outcome is very good.[3]
- Surgical removal by en bloc resection works with 1 or 2 cilia per eyelid.[1-4]

Ectopic cilia are hairs or a bundle of hairs growing through the conjunctival surface of the upper eyelid at the base of the meibomian/tarsal gland. They are usually located near the center of the lid and 3 to 4 mm from the eyelid margin. They are rarely seen on the lower eyelid. Clinical signs are blepharospasm and lacrimation (epiphora) and occasionally an ulcerative keratitis. Treatment is by electroepilation, en bloc conjunctival resection, or cryoepilation.[1,3]

MEDIAL CANTHUS SYNDROME IN NORMAL-ORBIT DOGS

This is different than the syndrome just described because it usually has only one or two eyelid abnormalities, and the eyes are much less at risk for vision threatening sequelae. It can affect most breeds with normal orbital conformation; however, the most common breeds affected in the author's experience are golden retriever, Labrador retriever, Rottweiler, Great Dane and the American cocker spaniel. It presents with tear overflow (or epiphora) without any ocular irritation or inflammation. A furrow can develop in the medial canthus which directs tears down the face, instead of allowing the tears to go down the nasolacrimal punctum. The dogs affected often have a shallow, sloping stop (nose conformation), and more subcutaneous fat on the dorsum of the nose than other dogs of that breed. The nasolacrimal punctum may be placed more ventral than usual in the conjunctival fornix, and should be checked for patency and size, as sometimes they are constricted. Some of these dogs have distichia, and medial conjunctival and nasal caruncular trichiasis.

The diagnosis is made from the examination, ruling out all other eye and eyelid diseases and observing the tears following this "gutter-like" furrow to drain down the face. This problem may be unilateral. Some of the dogs will outgrow it as their head size and shape matures.

Treatment is to treat any trichiasis or eyelash diseases if present, and dilate the punctum if it is small. Medial canthal V-plasty[4] for medial inferior entropion may encourage the tears to drain properly. This should not be done until the dog is mature and the eyes, head and palpebral fissure have finished developing.

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A MEDLEY OF FELINE OPHTHALMIC DISEASES

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Ocular disease in cats is most frequently associated with feline herpesvirus-1 (FHV-1). FHV-1 (viral rhinotracheitis) is by far the most contagious infectious disease of domesticated cats. It is a primary conjunctival pathogen and a secondary upper respiratory pathogen. It is serologically evident in up to 80% of cats worldwide. Approximately 80% of cats exposed to FHV-1 become latently infected following primary infection; reactivation of latent virus occurs in 50% of cats. Latency occurs in neurosensory tissue (trigeminal ganglion) and reactivation occurs after endogenous stress (hospitalization, parturition, lactation, boarding, increased photoperiod) or after exogenous corticosteroids are administered. Latency may also occur in corneal stromal cells or epithelial cells.

Ocular infection by FHV-1 is divided into those disease entities, which affect either ocular epithelial tissue or ocular stromal tissue; an immune response to viral proteins also plays a role in clinical signs of disease and is included under Stromal Disease (below):

Epithelial Disease	Stromal Disease
Infectious conjunctivitis	Stromal keratitis
Symblepharon	Corneal sequestrum
Punctate keratitis	Eosinophilic keratitis
Dendritic keratitis	Keratoconjunctivitis sicca
Geographic keratitis	Iridocyclitis (anterior uveitis)

FHV-1 CONJUNCTIVITIS

FHV-1 is the most common cause of conjunctivitis in cats. The disease is usually bilateral in young cats and unilateral in adult cats. Upper respiratory signs are accompany conjunctivitis in young cats. Blepharospasm and a serous ocular discharge that becomes mucoid to mucopurulent is typical. Conjunctival hyperemia becomes extreme but conjunctival edema is mild. Conjunctival necrosis may occur in neonatal and adolescent kittens and predisposes to development of symblepharon. Conjunctivitis typically has a clinical course of 14 to 20 days, is usually self-limiting, but persistent infection is possible.

Diagnosis: The diagnosis is based on clinical signs and/or by polymerase chain reaction (PCR) analysis. Immunofluorescent assay (IFA) testing of conjunctival scrapings has very poor sensitivity. Serology is also poor because of the marked seroprevalence of FHV-1 in the cat population. I do not perform diagnostic testing when conjunctivitis is mild—only for severe acute or chronic cases. Immunosuppression (FIV, FeLV, stress, treatment with corticosteroids or immunosuppressive drugs) may be considerations in chronically affected cats.

Treatment: For mild conjunctivitis, topical antibiotic (triple antibiotic, tobramycin, chloramphenicol) is prescribed to control secondary bacterial infection. If upper respiratory signs are present, an oral antibiotic is recommended. Antiviral treatment is reserved for cats with severe acute/chronic conjunctivitis, or when ulceration of the conjunctiva is present. Topical cyclosporine has been shown to have a profoundly adverse effect on ocular viral infection; it should never be used without antivirals.

SYMBELPHARON

Viral cytolysis results in ulceration and exposure of the underlying substantia propria. Symblepharon develops when two epithelialized surfaces ulcerate (one of which must be the conjunctiva) and the substantia propria of these surfaces adhere to each other. The most severe symblepharon occurs in pediatric/adolescent cats. Surgical correction of symblepharon is frequently unsuccessful because symblepharon reoccurs.

KERATOPATHIES

Specific clinical keratopathies occur in association with or as a direct result of FHV-1 infection. Clinical signs depend on the corneal tissue affected (epithelium vs. stroma) depth within the cornea, chronicity, and severity of infection.

Punctate (Microdendritic) Keratitis

This clinical presentation is characterized by multifocal, punctate opacities of the superficial epithelium (and occasionally the stroma) and represents acute reactivation of latent virus. Corneas will stain with rose bengal and may occasionally stain with fluorescein. Blepharospasm and serous ocular discharge that may become mucopurulent from secondary bacterial infection is common. Diagnosis relies on clinical appearance, PCR analysis, and response to treatment with antiviral medication.

Dendritic Keratitis

Branching corneal erosions of the corneal epithelium are the hallmark lesions of dendrites and is attributable to reactivation of latent virus. Clinical signs are considered pathognomonic—linear, branching or coalescing punctate erosions (rose Bengal positive), or ulceration (fluorescein positive).

Diagnosis: Diagnosis is made based on clinical signs (dendrites).

Treatment: Antiviral therapy is *always* indicated when viral keratitis is evident. Topical antivirals (idoxuridine 0.1%) is recommended every 2 hours for 24 hours, then every 4 hours until the erosions resolve, then every 6 hours for 2 weeks. Dilute Betadine Solution (1:20 to 1:50) sterile water:Betadine Solution (NOT SOAP) can be used topically 4 to 6 times daily. L-Lysine (500 mg PO, q 12h) competitively opposes arginine for incorporation into viral DNA, causing faulty viral replication. Owners should be warned to avoid using lysine products that contain propylene glycol (preservative) as it can induce Heinz-body anemia. Alpha interferon administered topically inhibits cell-to-cell transfection by herpesvirus. Oral dosing is not recommended since alpha interferon is degraded immediately by gastric enzymes and therefore NOT absorbed by the GI tract (when given orally, pharyngeal lymphatic tissue absorption is responsible for its effect).

Geographic Keratitis

Dendritic erosions may coalesce to form geographic (map-like) lesions. These lesions affect large areas of corneal epithelium, not stroma. Treatment recommendations parallel those described under "Dentritic Keratitis."

Stromal Keratitis

Stromal keratitis occurs in a small percentage of chronically and latently infected cats. Corneal ulceration and chronic viral shedding precede stromal involvement. Stromal keratitis readily develops in FHV-1–infected cats that are treated with topical steroids or cyclosporine. Stromal opacification and blindness caused by severe edema, vascularization, cellular infiltration, and fibrosis are common.

Treatment: Topical antiviral medication is usually unrewarding. Topical corticosteroids should be used only as a last resort and should never be used without concurrent antiviral treatment (may predispose to conjunctival or corneal epithelial disease). Topical treatment with idoxuridine and corticosteroids significantly decreases stromal disease if initiated early. Orally administered L-lysine is also recommended. If a sighted eye is desired, corneal transplantation may be done after resolution of vascularization. Topical cyclosporine may be a useful alternative or adjunctive treatment, but should never be used without concurrent antiviral medications.

CORNEAL SEQUESTRUM

A disease of stromal collagen that is unique to cats, the clinical appearance of corneal sequestrum is classical and unmistakable. The lesion is initially located in the superficial stroma and is circular or oval in shape. It begins as a light brown to amber colored, translucent nebula. As it progresses, it becomes dark brown to black. It may extend to the depth of Descemet's membrane, but midstromal depth is most common. Neovascularization and perilesional edema are usually severe. The epithelium may be present over the tan lesion, but invariably will ulcerate over black sequestrum. Occasionally the epithelium may undermine the periphery of a black lesion and result in spontaneous sloughing of the sequestrum. A serous ocular discharge with brown tear color is common. Conjunctival hyperemia, mild chemosis, blepharospasm, elevated third eyelid, and decreased physical activity are common signs. There is no age, gender, or breed predilection. Approximately 55% of sequestra are positive for FHV-1 DNA by PCR.

Treatment: Some ophthalmologists recommend monitoring the sequestrum for spontaneous sloughing, and perform surgery only if the lesion begins to progress deeper into the corneal stroma. Sloughing may not occur for weeks to many months. Other ophthalmologists recommend immediate surgical intervention. Surgical excision substantially shortens the course of the disease and should be performed whenever ocular discomfort is evident in an affected cat. Lamellar keratectomy and corneoconjunctival lamellar transposition are recommended. Corneas with deep sequestra should be considered for corneal transplantation. NOTE: Corneas may perforate when attempting removal! Medical treatment consists of treating with a topical antibiotic, atropine, antiviral drugs and a systemically administered, broad-spectrum antibiotic (if perforation is anticipated). Recurrence rates of up to 12% have been reported after excision.

EOSINOPHILIC KERATITIS

The corneal stroma becomes infiltrated with eosinophils, mast cells, plasma cells, lymphocytes, and neutrophils. One or both eyes may be affected. The lesion can vary in size and extent but usually is proliferative, white to pink, raised, vascularized mass that originates from the superior or temporal corneal limbus, but other areas may be affected. Plaques with a white "cottage cheese-like" appearance and consistency may be observed overlying the affected cornea. Perilesional corneal edema is frequently present. The corneal epithelium is usually intact but ulceration may occur. Conjunctival hyperemia, intermittent blepharospasm, and epiphora are common. Cats usually do not attempt to rub at affected eyes frequently. An age, breed, or gender predilection is not evident. A seasonal incidence has been suggested (higher incidence during spring and summer).

Diagnosis: A tentative diagnosis is made based on history and clinical appearance of the lesion. Cytologic examination of corneal scrapings shows numerous eosinophils, occasional mast cells, and numerous eosinophil major basic protein granules; 76% of affected cats are PCR positive for FHV-1 DNA.

Treatment: In addition to antiviral treatment described previously, topical corticosteroid treatment (every 6 hours) also results in rapid resolution. However since a high percentage of cats with eosinophilic keratitis are positive for FHV-1 (76%), concurrent treatment with topical antiviral drugs is recommended to prevent conjunctival or corneal epitheliopathy by virus reactivation. Orally administered megestrol acetate (2.5–5 mg PO every 24 hours for 5 days, then 5 mg once weekly for 1 month as needed to maintain "remission") is also effective. Orally administered corticosteroids have less of an effect on eosinophilic keratitis. CAUTION: Iatrogenic diabetes mellitus, pancreatitis, myelo-suppression, pyometra, hepatopathy, gynecomastia, and behavioral abnormalities may occur from treatment with megestrol acetate. Recurrence is common and may be attributable to spontaneous reactivation of latent FHV-1 infection. L-lysine administered orally (500 mg PO every 12 hours) is also recommended.

KERATOCONJUNCTIVITIS SICCA (KCS, "DRY EYE")

FHV-1 infection is the most common cause of dry eye in the cat. Viral destruction of the lacrimal gland or lacrimal ductules, causing ductal occlusion, or primary viral adenitis of the lacrimal gland is the proposed mechanism. Clinical signs vary with chronicity, but are generally mild and therefore frequently overlooked. The ocular discharge is initially serous in the very early stage of the disease. Ocular discharge may become mucoid to mucopurulent in the chronic stage but is never comparable to the discharge observed in canine KCS. Conjunctival hyperemia and thickening are usually evident but do not compare in severity to that of the dog. The cornea may appear lackluster, but vascularization, fibrosis and pigmentation rarely occur in the cat.

Diagnosis: Diagnosis is based on clinical signs; Schirmer tear test values are of little use in diagnosis of dry eye in cats because STT values in stressed cats are very low.

Treatment: Most cats with KCS attributable to FHV-1 infection do not have permanent or long-standing KCS. As the virus undergoes latency, tear volume usually improves and clinical signs often resolve. Supportive treatment is indicated during the active disease process. Topical artificial tearfilm replacement products (preservative-free, high viscosity) should be administered every 6 hours until clinical signs improve (response is usually seen within 2 weeks). Avoid using tear preparations with preservatives, especially benzalkonium chloride, EDTA, and Poly-Quad--they destroy the mucoid or oil layer of tear film. Topical antibiotic solution or ointment should be administered if corneal ulceration is present. Avoid use of topical atropine as it will decrease aqueous production further. Avoid use of mucolytic drugs (*N*-acetyl cysteine, Mucomyst). These drugs are not necessary and may be contraindicated. Topical use of cyclosporine or tacrolimus is recommended only in combination with topical antiviral drugs.

FHV-1 IRIDOCYCLITIS

Recent evidence suggests that "idiopathic" anterior uveitis in cats may in part be due to FHV-1. The specific cause of iridocyclitis is unknown ("idiopathic") in approximately 50% of cats with iridocyclitis. In 14% of these cats, FHV-1 DNA was detected in aqueous humor (centrifugal axonal transport mechanism via ophthalmic branch of the trigeminal nerve). In 50% of cats with idiopathic iridocyclitis, local production of FHV-1 antibody was detected. Clinical signs of uveitis vary with severity and chronicity. Acute iridocyclitis is characterized by engorged iris vasculature, miosis, aqueous flare and cell, decreased intraocular pressure (IOP), and potentially posterior synechia. Chronic iridocyclitis is characterized by hyperpigmentation of the iris, rubeosis iridis (neovascularization of the iris) and keratic precipitates. Numerous other clinical signs are also possible but are less frequently observed.

Diagnosis: First rule out other common causes of iridocyclitis in cats (FeLV, FIV, FIP, toxoplasmosis, bartonellosis). Aqueous paracentesis can be done for analysis of *T. gondii*–specific or FHV-1 specific antibody titers.

Treatment: Treatment should include administration of topical corticosteroids (1% prednisolone acetate) every 1 hour to every 6 hours and topical atropine every 12 hours to every 24 hours concurrently with antiviral treatment. In known or suspected cases of herpetic iridocyclitis, concurrent treatment with L-lysine is also warranted. When iridocyclitis is severe or chronic in nature, it can result in secondary glaucoma.

GLAUCOMA

Secondary (uveitic) glaucoma is far more common in cats compared with primary glaucoma. Lens instability associated with chronic uveitis or uveitic glaucoma is recognized far more frequently in cats than in dogs. It has been proposed that chronic lymphocytic-plasmacytic inflammation results in inflammatory zonulysis and subsequently lens instability. Other common causes of secondary glaucoma in the cat include intraocular neoplasia (melanocytoma, iridociliary adenoma, lymphoma, and chronic cataracts.

An interesting type of glaucoma that has been recently described in cats is called *ciliovitreal glaucoma* or *aqueous misdirection glaucoma*. This occurs because aqueous humor is directed in a posterior direction (into the vitreous chamber) instead of in an anterior direction (in the posterior and anterior chambers). This displaces the lens-iris diaphragm in an anterior direction which effectively narrows the iridocorneal drainage angle and results in narrowing or collapse of the ciliary cleft. The anterior chamber of affected eyes has a narrow depth. Anterior chamber depth is best evaluated by gaining a lateral vantage point (evaluating the profile of the cornea and lens-iris diaphragm) while directing the light along the visual axis (through the pupil).

In general, the clinical signs associated with glaucoma in cats are subtle compared with clinical signs that occur in the dog—therefore making the appropriate diagnosis can be challenging. Episceral injection and corneal edema are subtle and seldom recognized. Pupillary dilation is a common clinical sign of glaucoma in the cat. Unfortunately, most cats with glaucoma are not presented for evaluation until the affected eye has developed buphthalmos (absolute enlargement of the globe secondary to glaucoma). Although a buphthalmic eye in a dog is usually irreversibly blind, it is important to note that a buphthalmic eye in a cat often times remains sighted. However, detecting buphthalmos is more difficult in the cat compared with the dog because the feline orbit is deeper and has a more complete anterior orbital rim, and the eyelids tend to cover more of the anterior portion of the globe. Treatment of glaucoma necessitates use of drugs to decrease aqueous humor production and increase the facility of aqueous humor outflow. Use of miotic drugs is usually not indicated in treatment of feline glaucoma simply because of the associated inflammation. It is critical to treat with topical anti-inflammatory drugs while concurrently treating with anti-glaucoma medications.

References are available from the author upon request.

CORNEAL DEGENERATIONS

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Corneal degenerations always occur secondary to pathologic processes of the cornea and have a wide variety of clinical appearances. Corneal degenerations are typically unilateral but can be bilateral, and typically have associated clinical signs of inflammation present, (corneal neovascularization, melanosis, edema, disruption of the corneal epithelium, stromal fibrosis). Lesions may appear very similar to lesions of corneal dystrophy (located axial or paraxial) but the hallmark sign of degeneration is inflammation. Cholesterol/lipid or calcium deposits are present but infrequently impair functional vision. Certain physiologic states or concurrent systemic/metabolic diseases may result in calcium or lipid metabolic imbalance:

- Hypothyroidism
- Hyperadrenocorticism
- Diabetes mellitus/ketoacidosis
- Metabolic acidosis
- Post-prandial
- Pancreatitis
- Liver disease
- Primary hyperlipidemia (miniature schnauzers)
- Pregnancy
- Nephrotic syndrome
- Gram-negative sepsis

When cholesterol or neutral fats are involved in the degeneration, a reduction in dietary fat may decrease the size of the lesions(s) or may completely resolve the opacities. Topical corticosteroids are of no benefit and may exacerbate corneal opacification. Surgical excision may be necessary if vision is compromised.

CORNEAL DYSTROPHIES

By definition, corneal dystrophy is a primary, bilateral, hereditary, disorder that does not initially occur in association with corneal inflammation (neovascularization, edema, pain). Corneal dystrophies are typically slowly progressive and are not associated with systemic or metabolic disease processes. Dystrophy refers to abnormal or defective nutrition (metabolism) at the cellular or subcellular level. Dystrophies are classified based on their anatomic location within the cornea and are relegated to the corneal epithelium, stroma, or endothelium.

Epithelial Dystrophy

- Spontaneous chronic corneal epithelial defect (SCCED, indolent ulcer, basement membrane dystrophy) - Discussed under Ulcerative Keratitis.
- Punctate corneal dystrophy (shelties, dachshunds) - Discussed under Ulcerative Keratitis.

Both diseases can result in ulcerative keratitis, but the underlying pathogenesis is thought to be a form of epithelial dystrophy.

Lipid Dystrophy

Lipid corneal dystrophy occurs in many breeds; most notable are the Siberian Husky, Beagle, Airedale terrier, Golden retriever, and Cavalier King Charles Spaniel. Lesions are often bilaterally symmetrical, white-gray or silver, crystalline opacities. They may occur in the epithelium, subepithelium, stroma, or endothelium. The lesion is typically located in the axial or paraxial cornea, and may appear circular, oval, or "half-moon" in shape. The margin is sharply delineated and the corneal epithelium is intact overlying the opacity (ie, it will not stain with fluorescein). Neutral lipids, cholesterol, and phospholipids comprise the opacities. Differentiate from scar tissue (dystrophies get larger and scars get smaller over time). Treatment (surgical removal) is usually not necessary.

Endothelial Dystrophy

Corneal edema is the hallmark sign in endothelial dystrophy. Older dogs, Boston terriers, and chihuahuas are at risk of developing endothelial dystrophy. As the cornea becomes progressively thicker (edematous), it becomes bluish-white in appearance and corneal vascularization is absent. The condition is bilateral but one eye may become significantly more opaque prior to the fellow eye. Epithelial and subepithelial bullae may be observed and may rupture through the epithelium, creating an ulcer and typical signs of pain. When ulceration is present, it should be treated (see section on superficial ulcers). Treatment with topical hypertonic ophthalmic medications (5% NaCl) is indicated when bullae are present, but will not result in significant resolution of corneal edema. Thermokeratoplasty (dogs) and penetrating keratoplasty [corneal transplant] (cats) are the only definitive treatments.

ORBITAL DISEASE IN DOGS AND CATS

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Orbital disease is common in dogs and cats but may be misdiagnosed and subsequently treated inappropriately. Knowledge of normal orbital anatomy and common specific diseases for each species is required to understand which specific abnormality may be affecting the orbit.

A complete history and thorough physical examination are prerequisites to the diagnostic workup of all orbital diseases. When orbital disease is suspected, history should always include the onset and duration of the abnormality, any change in eating behavior or difference in temperament and a there has been a change in visual performance. The orbit is a confined space that has no room for expansion or enlargement of its contents. Since the orbit cannot be examined directly, signs of orbital disease are evident indirectly. Disorders are characterized by clinical signs that alter the function, appearance, or position of the globe, eyelids or ocular adnexal structures. Compare the size of palpebral fissures, observe eyelid carriage, position of eyelids and nictitating membrane, location and mobility of the globe within the orbit and the presence of ocular discharge. Palpation of the periorbital areas is recommended. Retropulsion of the globe into the orbit through the closed eyelid should be done—the globe is retropulsed normally a space occupying orbital lesions is not present. Carefully examine the oral cavity with particular attention to periodontal/dental structures—general anesthesia may be needed (periodontal probe/dental explorer). Neuro-ophthalmic examination is also recommended.

CLINICAL SIGNS OF ORBITAL DISEASE ARE DIVIDED INTO PRIMARY AND SECONDARY SIGNS

Primary clinical signs include:

1. Exophthalmos—anterior displacement of the globe that is not associated with increased globe size.
2. Enophthalmos—posterior displacement of the globe.
3. Strabismus—involuntary deviation of the globe from the primary position.

Secondary clinical signs include (not all-inclusive):

1. Conjunctival hyperemia
2. Chemosis
3. Swelling of lids and periorbita
4. Elevation of the nictitating membrane
5. Pain upon opening the mouth
6. Mild elevation of IOP
7. Lagophthalmos
8. Exposure keratitis
9. Abnormal PLR
10. Visual impairment
11. Scleral indentation
12. Facial asymmetry

Pathologic processes affecting the orbit involve one or more of three anatomic compartments:

1. Intraconal (within the extraocular muscle cone);
2. Extraconal (outside the cone but inside the periorbita)
3. Inside the orbit but outside the endorbita (periosteum).

When trying to determine which anatomic compartment of the orbit is affected, observe the direction of displacement of the globe/orbital structures. Intraconal mass lesions result in axial exophthalmos but infrequently cause elevation of the nictitating membrane unless extremely large. Extraconal mass lesions almost always result in protrusion of the nictitating membrane. Strabismus and/or displacement of the globe is usually opposite in direction to the location of the mass. Mass lesions located outside the endorbita may mimic extraconal masses but usually are associated with nasal or paranasal sinus disease.

RULES REGARDING DISPLACEMENT OF THE GLOBE

Rule#1—The direction of displacement is generally opposite the location of the mass effect:

- Lateral displacement = medial mass effect.
- Medial displacement = lateral mass effect.
- Dorsal displacement = ventral mass effect.
- Ventral displacement = dorsal mass effect.
- Axial anterior displacement = posterior mass effect.

Exceptions to Rule #1:

- Axial posterior displacement = loss of posterior orbital tissue.
- Medial displacement = loss of medial orbital wall.
- Ventral displacement = loss of orbital floor.

Rule #2—An intraconal mass infrequently causes elevation of the nictitating membrane.

- Exception to Rule #2: A large intraconal mass.

Rule #3—Extraconal mass effect frequently causes elevation of the nictitating membrane.

- Exception to Rule #3: Fibrosing/cicatrizing lesions involving the nictitans.

CLASSIFICATION OF ORBITAL DISEASES

Orbital disease is broadly classified as primary veruss secondary, and as inflammatory, neoplastic, cystic, or rarely other (vascular anomaly, congenital malformation, etc.). Inflammatory diseases may affect animals at any age. There may be a history of refusing to eat dry dog/cat food. Anorexia and weight loss may be evident. Acute onset of clinical signs and behavioral /temperament change is typical. Clinical sign of pain may be present—resistance to opening the mouth. The coronoid process of the mandible impinges on the orbital tissues when the mouth is opened. Animals may be febrile but a leukocytosis is usually absent. Neoplastic orbital diseases usually affect middle-aged to older animals (mean age of dog 8 years; mean age of cat 8.9 years) and have a history of slowly progressive onset of clinical signs and are generally not painful. Exceptions are mast cell tumor, lymphoma, or rapidly growing neoplasms which outgrow their vascular supply and, as the neoplasm undergoes necrosis, recruitment of inflammatory mediators occurs. Cystic orbital diseases are less common and may affect any age, may have acute or insidious onset of clinical signs and are usually nonpainful.

SELECTED INFLAMMATORY ORBITAL DISEASES

Orbital Cellulitis/Abscess

Tooth root abscess from periodontal or endodontic disease are the most common cause of orbital cellulitis/abscess in dogs and cats. Trauma, extension of sinusitis, bone sequestration, oral foreign bodies (animal chewing on bones/stick, etc) may also result in orbital abscess. Onset of clinical signs is usually rapid and include fever, pain upon opening mouth, chemosis, and exophthalmos. A soft, fluctuant swelling present behind the last molar is reported as typical in the literature, but is actually uncommon. Periodontal or endodontic diseases of the maxillary PM3, PM4, M1, and M2 can cause orbital or periorbital disease. Effective treatment consists of establishing surgical drainage and systemic antibiotics. The classic workup of a suspected orbital abscess is orbital echography, oral examination with a dental explorer and periodontal probe, and dental radiographs. If test results reveal dental disease, drainage should be established by extracting the affect tooth and allowing drainage to occur through the alveolus, NOT by creating an incision caudal to the maxillary second molar tooth. Culture/susceptibility testing should be considered. Systemic antibiotics should be administered and treat exposure keratitis/iridocyclitis if present.

Masticatory Muscle Myositis (MMM)

Masticatory muscle myositis occurs most frequently in the Golden retriever, Weimaraner, Shetland sheepdog, and German shepherd, but many other breeds may be affected. The disease involves the masseter, temporalis, and pterygoid muscles (ie, muscle of mastication—those muscles innervated by CN V3). Clinical signs of the acute form of the disease include exophthalmos (uni- or bilateral), eyelid edema, protrusion of the third eyelid, conjunctival hyperemia, and pain upon opening the mouth. Masseter and temporalis muscles are typically firm and painful upon palpation. The medial pterygoid may also be palpated through the roof of the mouth caudal and medial to the maxillary teeth. Acute inflammation may last 10 to 21 days and frequently recurs. Chronically affected have atrophy of the temporalis, masseter, and medial pterygoid muscles, resulting in enophthalmos and elevation of the nictitating membrane. Affected dogs may also develop trismus and may not be able to prehend food. Examination of temporalis muscle biopsy shows lymphocytic infiltration and type IIM myofiber antigen-antibody complexes. Serum may be sent if biopsy is not possible. Antibody directed against type IIM myofibers (619-534-1537; Dr. Diane Shelton, Comparative Neuromuscular Laboratory). Serologic diagnosis is positive in 86% of dogs with the acute inflammatory form of the disease, unless they have been treated with corticosteroids. Serologic diagnosis is also much less lilely to be made in dogs with the chronic form of the disease. Immunosuppressive doses of corticosteroids (2 mg/kg q 12 h) for a minimum of 21 days is recommended prior to decreasing the dosage. Although clinical response to treatment may be dramatic in 3 to 5 days, do not decrease the dosage prior to 21 days, then taper slowly over the next 2 months. Azathioprine may also be effective (2 mg/kg every 24 hours). Feed a gruel diet and treat exposure keratitis if present.

Extraocular Polymyositis

This disease was recently described in Golden retrievers, Dobermans, Springer spaniels (field-trial skull conformation). Signs include acute onset of bilateral exophthalmos, chemosis, 360° scleral show; 80% of affected dogs are 7 to 10 months old, with a 2:1 female:male ratio. High correlation is seen with physiological stressors (estrus, OHE, neutering, boarding at kennels), with acute onset of bilateral exophthalmos, no elevation of the nictitating membrane, and no signs of pain. There is usually mild to moderate resistance to globe retropulsion and occasionally compromised vision occurs (diplopia). There is a high rate of recurrence with subsequent heat cycles, stressors, etc. Diagnosis is based on clinical signs, CT/ MRI, and extraocular muscle biopsy; serology has been unrewarding. Treatment parallels that described for Masticatory Myositis (above).

NEOPLASTIC ORBITAL DISEASE

Neoplastic orbital disease is far more common in dogs and cats compared with inflammatory or cystic orbital disease. Signs of orbital neoplasia usually progress slowly and may develop insidiously and evade perception until the disease is considerably advanced. Orbital neoplasms in dogs and cats historically have had a stigma of poor prognosis attributable to the late presentation of affected animals for treatment and the malignant nature of orbital neoplasms. Whereas primary tumors constitute the majority of orbital neoplasms in dogs, secondary neoplasms are most frequently reported in cats (extension from neighboring tissues—nasal cavity or paranasal sinuses). 91% of orbital tumors in dogs and 90% in cats are histologically classified as malignant. The most common clinical sign is slowly progressive unilateral exophthalmos. Pain is not a prevalent sign upon opening the mouth, and fever or leukocytosis are usually absent. Only orbital lymphoma and mast cell tumor are neoplasms that are characterized by rapid onset and cause pain. These two neoplasms may also affect animals at fairly young ages. The average age at diagnosis for dogs and cats is 8 and 8.9 years, respectively. It is virtually impossible to differentiate the different types of orbital neoplasia by imaging modalities. Oral examination, orbital ultrasound, fine needle aspirate, CT scan, MRI, and +/- chest radiographs are indicated to determine the extent/boundaries of the neoplasm. Fine needle aspiration or exploratory orbitotomy for biopsy is usually necessary to determine the specific type of neoplasm present. Adjuvant treatment depends on the type of neoplasm, extent of involvement, and whether or not metastases are present. Whenever orbital surgical intervention is considered, the surgeon should: 1) Ascertain the type of neoplasm (fine needle aspiration biopsy, biopsy), 2) Determine the extent of the neoplasm (define boundaries), 3) Be completely familiar with orbital anatomy, 4) Anticipate surgical or postoperative complications, 5) Realign any unrealistic expectations the client may have.

CYSTIC ORBITAL DISEASE

Cystic structures may arise from the orbital lacrimal gland, gland of the nictitating membrane, zygomatic salivary gland, mucosa of the paranasal sinuses, or from retained or buried conjunctival mucosa. Cysts frequently appear pale gray-blue in color, are usually firm and smooth, and tend to have a distinct plane between normal orbital tissues and the external cyst wall. Cyst contents may be serous or viscous, clear or rust-colored, and may spontaneously dissect into the oral cavity. To facilitate extirpation, blunt micro-dissection should be done completely around the cystic mass prior to aspiration and evacuation of the cyst cavity. Dissection is difficult after a cystic structure is collapsed. Cystic structures of lacrimal tissue origin may also be marsupialized to the conjunctival surface to promote drainage. Cystic tissues should be examined histopathologically to detect cystic neoplasms of orbital tissue origin.

Orbital diseases in dogs and cats can be difficult to differentiate based on clinical appearance alone. Obtaining a detailed history and performing a thorough physical (specifically ophthalmic and oral examination) frequently reveals abnormalities to direct further specific diagnostic testing. Inflammatory orbital disease generally carries a favorable prognosis, but the prognosis for neoplastic orbital disease is grave.

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TIPS TO PERFORM A VIRTUOUSLY BLOODLESS ENUCLEATION

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Hemorrhage that occurs during enucleation surgery is commonly encountered and can substantially delay completion of the surgical procedure. However, the following techniques are rapid, inexpensive, and can be employed to substantially reduce or even eliminate hemorrhage during enucleation or evisceration surgery. These techniques do not require specialized instrumentation, placement or vascular ligatures during enucleation surgery, or use of cautery.

GRAVITY

Dependent forces may be used to reduce hemorrhage. The surgical table is raised 15 degrees to elevate the patient's head and the eye is prepared for aseptic surgery.

LOCAL INFILTRATIVE ANESTHESIA

After induction of general anesthesia, the use of local anesthesia will induce local orbital hemostasis and tissue intumescence. It will also provide local anesthesia for up to 10 hours after surgery and provide effective pain-free postoperative recovery. The surgeon must avoid inducing the oculocardiac reflex (profound bradycardia or standstill) by premedicating with glycopyrrolate or atropine. A solution of 1 part lidocaine 1% or 2% and 4 parts bupivicaine 0.5% containing epinephrine (1:100,000) is made for infiltrative injection. I routinely draw up 1 mL lidocaine and 4 mL bupivicaine for a total of 5 mL anesthetic solution. Do not exceed 5 mg/kg lidocaine or 1.5 mg/kg bupivicaine (a factor in with very small dogs/cats). A 25-gauge 5/8-inch needle is then attached to the syringe and the subconjunctival space is infiltrated with 0.35-0.5 mL of the solution. A 22-gauge 1-inch or 1½-inch needle is then used for retrobulbar infiltration. The needle is passed through the palpebral conjunctiva between the lower eyelid and orbital rim. As the needle is advanced in a posterior direction, the entire needle is swept side-to-side in a horizontal motion while the needle is being advanced past the equator of the globe. As the needle tip is advanced past the equator, the angle of advancement is reduced so that the needle tip resides in the extraorbital space posterior and ventral to the globe. The syringe is then aspirated to assure that an intravascular compartment has not been entered, and approximately 1.5 to 2.0 mL of the solution is injected. A second infiltration is then repeated with an entry point near the lateral canthus. The needle is again passed through the palpebral conjunctiva between the lateral canthus and the lateral orbital ligament. As the needle is advanced in a posterior direction, the entire needle is swept up-and-down in a vertical motion while the needle is being advanced past the equator of the globe. The needle tip will enter the endorbita. The syringe is again aspirated to assure that an intravascular compartment has not been entered and 1.5 to 2.0 mL of the solution is injected. Digital retropulsion of the globe is then done several times to disperse the injected solution.

TISSUE DISSECTION

The transconjunctival enucleation technique is then used as this substantially reduces tissue trauma and does no require transaction of the extraocular muscles (as occurs with the transpalpebral technique). The extraocular muscle attachments to the globe are then transected. The retractor bulbi and muscle and optic nerve are blindly transected.

If infiltrated correctly, hemorrhage will be minimal or even eliminated completely.

WHY YOUR CHERRY-EYE SURGERY "POPPED"

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Prolapse of the gland of the nictitating membrane ("cherry eye," "popped haw") occurs frequently in dogs and less frequently in cats. It is the most frequently reported primary abnormality of the third eyelid in the dog. The proposed mechanism for prolapse of the gland is weak or abnormal fibrous connective tissue attachments from the base of the gland to the ventral orbital rim. However, prolapse is likely multifactorial, and concurrent anomalies of the supportive cartilage of the nictitating membrane (scrolling), discernable clinical signs of keratoconjunctivitis sicca, and low-grade inflammation/hypertrophy of the gland may also contribute to prolapse. A distinct breed predisposition exists, with brachycephalic breeds being over-represented, but other breeds may also develop prolapse. Prolapse can occur unilaterally or bilaterally, and in my clinical experience, partial prolapse of the second eye is most common in dogs with a complete unilateral prolapse. In unilaterally affected dogs, manual retropulsion of the globe on the normal-appearing eye often causes the gland to partially prolapse; this gland may return to its normal orbital position when pressure is removed. This suggests impending complete prolapse of the gland and is reason to recommend preventive repositioning of the gland before complete prolapse occurs. In cats, unilateral prolapse is most common with the Burmese and Birman breeds being overrepresented.

It is important to note that all canine breeds that are predisposed to prolapse of the gland of the nictitating membrane are also predisposed to development of keratoconjunctivitis sicca (KCS, dry eye). Complete excision of a prolapsed gland is considered flagrant malpractice in such breeds because it predisposes affected dogs to develop KCS or at least hastens development of dry eye. For this reason, the preferred treatment is replacement of the gland. Restoration of the gland to its normal position preserves tear production. It is important to identify all contributing abnormalities to gland prolapse and to determine if the other "normal" eye has an impending gland prolapse. Scrolled cartilage of the nictitating membrane may occur concurrently with prolapsed gland of the nictitating membrane. In eyes with a prolapsed gland and concurrent abnormal cartilage of the nictitating membrane, surgical excision of the abnormal portion of cartilage is recommended during the same operative period. A scroll-like curling of the cartilage near the gland requires careful excision of the abnormally scrolled segment of cartilage. The rate of post-operative re-prolapse of the gland is much higher when abnormal cartilage is not excised concurrently with surgical repositioning. In cases of dry eye, always check the other eye.

The rate of postoperative re-prolapse of the gland is much higher in affected eyes with concurrent lymphoid follicle formation and/or hypertrophy of the gland. In these instances, it is prudent to treat topically with 0.1% dexamethasone or 1% prednisolone acetate ophthalmic suspension prior to attempting surgical repositioning of the gland. In some breeds (English Bulldog, Neopolitan Mastiff) despite topical treatment prior to surgery, hypertrophy of the gland seldom resolves and a higher rate of re-prolapse exists. In dogs with a prolapsed gland and concurrent discernable clinical signs of keratoconjunctivitis sicca, treatment with 0.02% tacrolimus or 1% cyclosporine is recommended prior to surgery.

Selection of the appropriate technique to reposition the prolapsed gland is critical to long-term success. There are at least eight primary surgical procedures that have been published for repositioning the prolapsed gland. All techniques described for surgically repositioning the gland include suturing the gland to: 1) adjacent sclera; 2) extraocular muscle tendon; 3) ventral endorbita of the orbital rim; or 4) conjunctival imbrication ("pocket" technique). The best technique to use in instances where the gland has recently prolapsed or has not been surgically replaced previously is the conjunctival imbrication modification of the Morgan pocket technique. This procedure is used most frequently among veterinary ophthalmologists because it has the highest success rate for maintaining the repositioned gland in its normal anatomic orbital space and also preserves and maintains normal tear production compared with other repositioning techniques.

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MANAGEMENT OF COMMON CANINE OCULAR EMERGENCIES

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Ocular emergencies in the dog are common in small animal practice. A thorough understanding of the eye and the clinical manifestations of different disease processes of the eye are important to proper diagnosis and treatment. Recognition and appropriate treatment of ocular emergencies may mean the difference between retention or loss of vision, and retention or loss of the eye. Below are some of the more common ocular emergencies likely to be encountered in the dog.

GLAUCOMA

Glaucoma, or an increase in intraocular pressure that affects function of the eye, can result from either primary or secondary causes. Primary glaucoma is especially common in the dog, particularly as an inherited trait in certain breeds. Primary glaucoma occurs when the iridocorneal angle and ciliary cleft are abnormal and aqueous humor can no longer egress from the eye adequately. While this can occur in mixed breed dogs as well, it is often noted in cocker spaniels, Bassett hounds, arctic breeds, chow chows, shar peis, and some terriers. Secondary glaucoma may occur with anterior uveitis, lens luxation, hyphema, and intraocular tumors.

Clinical Signs of Acute Glaucoma

Pain as evidenced by blepharospasm, tearing, elevated third eyelid, rubbing at eye, resentment of touch around the affected eye; conjunctival and episcleral hyperemia; corneal edema, dilated pupil with no pupillary light response, loss of vision in affected eye (negative menace response). In acute glaucoma the globe will be normal sized. When the eye becomes buphthalmic (enlarges) this is a sign of *chronic glaucoma*. Dogs also tend to be less demonstrative of pain when glaucoma becomes chronic than when it is acute, although their pain should not be discounted. Most dogs are irreversibly blind with chronic glaucoma.

Diagnosis of Glaucoma

Measurement of intraocular pressure (IOP) is imperative. Normal IOP in the dog is typically between 12 and 20 mmHg. In veterinary medicine the applanation (TonoPen) and rebound (TonoVet) tonometers are recommended.

Treatment of Acute Glaucoma

Reducing IOP as quickly as possible should be the goal of treatment. A variety of topical glaucoma drugs are available, some very good at reducing IOP. Drugs working by different mechanisms can be administered together, waiting approximately 10 minutes between drops.

Prostaglandin Analogs (PA): These are the newest miotic agents. Constriction of the pupil usually occurs within 1 hour of administration and dramatic decreases in IOP can be seen in some dogs within the first 1 to 2 hours. In addition to physically opening the iridocorneal angle through their miotic effect, prostaglandin analogs are thought to increase uveo-scleral outflow of aqueous humor, an alternative pathway. Examples include latanoprost (Xalatan), travoprost (Travatan), and bimatoprost (Lumigan). These agents can be used every 12 to 24 hours depending on the severity of the glaucoma. If the pupil does not move, as for example with synechia or chronic glaucoma in which the sphincter muscle is damaged, PAs may not significantly reduce IOP.

Carbonic Anhydrase Inhibitors (CAI): These drugs decrease aqueous humor production. The most common drug in this category used in dogs is dorzolamide (Trusopt). Brinzolamide (Azopt) is a similar drug. CAIs inhibit aqueous humor production and have their onset of action within a few hours. These agents should be used every 8 hours.

Beta Blocking Agents: These agents decrease aqueous humor production. The most common one used in the dog is 0.5% timolol maleate (available generically) and is recommended not as a sole agent but for use with other types of drugs (above). Timolol should be administered every 12 hours. At this frequency heart rates are not typically affected in the dog. Other beta blockers available are betaxolol (Betoptic) and levobunolol (Betagan). These latter two have not been well studied in the dog.

Hyperosmotic Agents: The use of prostaglandin analogs in dogs with acute glaucoma has lessened the need for hyperosmotic therapy and they should be employed first. If combinations of the above topically applied agents are unsuccessful at reducing IOP within 2 to 4 hours, mannitol can be administered. The dose is 1 to 2 g/kg given intravenously, over about 30 to 45 minutes. Water should be withheld for about 6 hours. Mannitol will create an osmotic gradient between the eye (primarily the vitreous body) and the vasculature, drawing fluid from the eye and reducing IOP. Effects can often be seen within 1 to 2 hours with a maximal effect seen at about 6 hours. Topical glaucoma drugs should be continued as the effects of mannitol will last no longer than 24 hours.

Other Agents: Older topical drugs such as pilocarpine, epinephrine, and demercarium bromide are used less often today with the advent of newer and more efficacious therapies. Oral CAI (acetazolamide, methazolamide, dichlorphenamide) have a wide variety of systemic side effects and have largely fallen out of use for this reason. The topical CAIs have no systemic side effects.

LENS LUXATION

The lens is free to move within the eye when the zonules which normally attach it to the ciliary body are broken. The most common reasons for canine lens luxation are primary (abnormal zonules, seen in terrier breeds) and secondary to hypermature cataracts. If the lens falls posteriorly into the vitreous cavity, there may be no immediate emergency. However, when it moves into the anterior chamber, it may cause acute pain and/or glaucoma.

Clinical Signs of Anterior Lens Luxation

Clinical signs include pain as evidenced by blepharospasm, tearing, elevation of third eyelid, corneal edema, and glaucoma.

Diagnosis of Lens Luxation

Diagnosis is by visualization of the lens in the anterior chamber or the vitreous cavity. If the cornea is severely edematous an ocular ultrasound may be needed to diagnose an anterior lens luxation. Intraocular pressure should always be measured.

Treatment of Lens Luxation

Initial therapy for an anterior lens luxation should include topical agents for treating glaucoma and uveitis, both of which are commonly associated with this disorder. Systemically administered analgesic and anti-inflammatory agents (NSAIDs, tramadol) are also helpful. Even if the IOP is not elevated, prophylactic therapy with agents such as dorzolamide and timolol are indicated. The miotic agents such as prostaglandin analogs should be avoided so as not to trap the lens in front of a closed pupil. Topical anti-inflammatory therapy (see Uveitis section) should be instituted with prednisolone acetate or dexamethasone as long as no corneal ulceration exists. The only definitive therapy for a lens luxation is surgical, so referral to an ophthalmologist should be recommended as soon as possible.

ACUTE UVEITIS

Inflammation of the uvea may involve iris and ciliary body (anterior uveitis) or choroid (posterior uveitis) or both (panuveitis). Anterior uveitis is more common. Underlying causes of canine uveitis can sometimes be difficult to pinpoint. All dogs with uveitis should have a thorough physical examination. A complete blood count (CBC), chemistry panel, and infectious disease titers should be considered based on each individual case and prevalence of infectious disease in the area.

Clinical Signs of Acute Anterior Uveitis

Clinical signs include pain, conjunctival and episcleral hyperemia, corneal edema, miosis, decreased intraocular pressure, aqueous flare, hyperemic iris, fibrin or blood (hyphema) or white blood cells (hypopyon) in the anterior chamber, and blindness in affected eye (especially if posterior uveitis is present as well).

Diagnosis of Acute Anterior Uveitis

Diagnosis is by visualization of some or all of the above clinical signs. Rule out glaucoma through measurement of IOP. Stain the cornea with fluorescein dye to check for ulceration.

Treatment of Acute Anterior Uveitis

Treatment should be very aggressive to manage ocular inflammation and pain. Topical corticosteroid therapy should be instituted (as long as no corneal ulceration is present) with either 1% prednisolone acetate (shake very well) or 0.1% dexamethasone, four to six times daily. Atropine for iridocycloplegia should be instituted at twice daily as long as IOP is low. If IOP is normal in the face of uveitis, glaucoma may already be developing and atropine should be avoided. Systemic anti-inflammatory agents such as NSAIDs or in severe uveitis, oral prednisolone at 1 to 2 mg/kg/day, should also be started. If posterior uveitis exists, only systemically administered agents will reach these tissues and oral prednisolone becomes imperative. If pain is severe, oral narcotic agents such as tramadol should also be administered. Dogs with acute uveitis should be re-examined in about 2 to 3 days. Therapies should be only gradually decreased as improvement is seen. IOP should be measured at every visit.

DEEP CORNEAL ULCERS

Deep corneal ulcers in dogs should be assumed to be infected with bacteria regardless of appearance. Most corneal stromal ulcers will have a purulent cellular infiltrate and associated uveitis. Very aggressive medical therapy is required to treat deep corneal ulcers. Once ulcers become descemetoceles, or if they fail to respond to medical therapy within a couple of days, surgery with a conjunctival graft will be needed to prevent corneal perforation.

Clinical Signs of Deep Corneal Ulceration

Clinical signs include pain, tearing (unless dry eye is present), conjunctival hyperemia, corneal edema and yellowish cellular infiltrate around the ulcer, variable corneal vascularization arising from the limbus, and miosis due to associated uveitis.

Diagnosis of Deep Corneal Ulceration

If profuse tearing is not evident check tear production with a Schirmer Tear Test (normal ≥ 15 mm/min) before administering any fluids to the eye. Visualization of above clinical signs; fluorescein staining (a stromal ulcer will take up fluorescein dye; a desmetocele will not absorb the dye on Descemet's membrane). If possible, a culture of the ulcer should be taken prior to treatment, although one cannot await results of a culture for treatment choices. Following proparacaine, the edge of the ulcer can be scraped gently and a cytologic preparation made to look for bacteria. Gram-positive cocci are the most common organisms infecting the canine cornea.

Treatment of Deep Corneal Ulcers

Two different broad spectrum antibiotic solutions should be chosen and alternated every hour for as much of the day as possible (see below for combinations); atropine (if dry eye not present) two to three times daily, oral NSAID therapy +/- tramadol for pain. If dry eye is present, cyclosporine ointment should be administered twice daily. Autogenous serum handled sterilely can also be helpful to arrest corneal melting – apply four to six times daily. A 1% to 2% compounded EDTA solution can also be used for corneal melting. Ointments should be avoided due to difficulty of administration and limited spectrum of choices.

- Antibiotic combinations recommended:
- Fluoroquinolone (ofloxacin or ciprofloxacin) + tobramycin
- Fluoroquinolone + neomycin-polymixin B-gramicidin
- Fluoroquinolone + cefazolin (made from lypophilized powder for injection: 100 mg/mL)

If therapy is effective the ulcer will stabilize and not look worse for the first 24 to 48 hours. After that gradual clearing of the purulent infiltrate and edema will be seen. Frequency of therapy should not be decreased too soon; although once it is clear the ulcer is healing antibiotic frequencies can be reduced to four times daily with each antibiotic. If the ulcer continues to worsen despite aggressive management, referral for surgery should be considered.

GLOBE PROPTOSIS

Proptosis of the globe is common in brachycephalic breeds with often surprisingly little trauma causing the event. Non-brachycephalic breeds with a proptosis have generally suffered severe head trauma. Unless the globe is badly damaged, repositioning of the eye should be attempted as enucleation can be performed later if warranted. Clients should be warned that dogs are usually blind in the proptosed eye (from optic nerve stretching) and that lateral strabismus (from a torn medial rectus muscle) is common.

Procedure for Repositioning Proptosed Globe

With dog under general anesthesia, gently clip periocular hair and cleanse skin with dilute betadine solution (not scrub) as well as the globe. Rinse well with sterile saline. Perform a lateral canthotomy to improve globe access. Place a sterile lubricant on the eye (such as KY) to protect cornea. Using forceps (such as Allis tissue) grasp upper and lower lids – have an assistant place gentle traction on the eyelids. Use a flat instrument such as a scalpel handle horizontally across the cornea. Apply gentle pressure against the cornea to move globe posteriorly as the assistant pulls the eyelids cranially in front of globe. The globe will often not fully reduce due to swelling and hemorrhage of retrobulbar tissues. Close lateral canthotomy. Place two horizontal mattress sutures (temporary tarsorrhaphy) half depth through the eyelids (so as not to have suture on the conjunctival surface rubbing cornea). Be sure to use stints (cut pieces of IV tubing work well) on the suture so it doesn't cut into eyelids. Leave enough space at the medial canthus for topical medications to be used.

Postoperative Care

Postoperative care may include use of an E collar; topical antibiotic solution (neopolygram; tobramycin) three times daily; oral NSAID; oral antibiotic such as amoxicillin or cephalexin. Recheck in 5 days to assess tarsorrhaphy sutures and any ocular discharge – if doing well, leave sutures in place for 2 weeks.

HYPHEMA

Blood in the anterior chamber may occur from trauma, uveitis, retinal detachment, intraocular tumor, or a bleeding disorder. A thorough physical examination should be performed to look for other signs of bleeding. An ocular ultrasound may be necessary to look for a retinal detachment if this history is not known. Intraocular pressure should always be measured in eyes with hyphema. Fluorescein staining of the cornea should be performed to check for ulceration.

Treatment of Hyphema

Topical corticosteroids (if no ulcer) are used as above for uveitis; and topical tropicamide 2X daily to move pupil; the use of atropine may increase chances of glaucoma. A systemic NSAID is used for pain and inflammation of the eye. Recheck in about 3 to 4 days, measuring IOP again. An eye that continues to have fresh blood has an ongoing bleed and this carries a poor prognosis. Bleeding from trauma will have clotted. Depending on how much fibrin is present, an intraocular injection of tissue plasminogen activator may be needed to dissolve fibrin. Contact an ophthalmologist as the window of opportunity only exists for approximately one week.